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CHRONIC DISEASES OF CHILDHOOD

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INTRODUCTION

PEDIATRICS developed as a special field of medicine when it was realized that infants and children were not merely small adults and that the diseases and pathologies of this period of growth presented marked differences from those of the mature adult. Mainly, the diseases of infants and children were acute and often more severe in their effect. While an understanding of nutritional requirements of infancy and childhood was essential, infant mortality was largely reduced by the prevention and effective treatment of acute infections, particularly of the enteric and respiratory systems.

Since World War II, pediatrics has presented a change in aspect. With the reduction in incidence and severity of acute infections, the chronic diseases emerge as of major importance. Investigations and research are now focused on these more difficult and less understood conditions. The role of genetics becomes increasingly important as we detect those defects, physical and/or metabolic, which follow a pattern of inheritance. Malignant conditions and sensitization states are recognized with greater frequency, and increasing attention is being paid to mental health.

It follows that the social aspects of the "new pediatrics" become more important, but also more complicated. Counselling and advice involve the family and the larger community in longterm planning.

This issue of the JOURNAL OF CHRONIC DISEASES presents a review of some of the important aspects to today's pediatrics, although it has not been possible to include all the major conditions or to discuss adequately the psychological, social, and economic aspects of present-day pediatric problems.

SUGGESTED READING

1. Keith, John D., Rowe, Richard D., and Vlad, Peter: Heart Disease in Infancy and Childhood, New York, 1958, The Macmillan Company.
2. Nadas, Alexander S.: Pediatric Cardiology, Philadelphia, 1957, W. B. Saunders Co.

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CHRONIC ENDOCRINOPATHIES IN CHILDHOOD

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ENDOCRINE gland problems in children are usually chronic; few are temporary. Many may be genetically conditioned, but environmental conditions influence their manifestations during life.

Only those chronic endocrinopathies will be discussed which have practical importance.

PITUITARY

Hyperpituitarism (gigantism) of the classical type is rare in childhood. Several cases due to an eosinophilic adenoma have been recorded. Occasionally the rapidly growing child will have a suspiciously enlarged sella turcica. In tall children one thinks of increased production of growth or somatotrophic factor (PSF) by the pituitary, but this is difficult to prove, since laboratory tests for growth hormone are not easily or reliably done. Today, children grow to be taller—in our area, 16-year-old boys are 3.3 inches taller than they were 70 years ago. The familial tendency to height could be due possibly to extra production of PSF. The occurrence of a unihormonal pituitary disturbance is seldom found; it is most frequently multihormonal. Tall noneunuchoid children (Neurath-Cushing syndrome) often have precocious evidence of pituitary gonadotropic (FSH) hormone production, evidenced by early appearance of pubic hair, axillary hair, growth of external genitals, breast growth, and early menarche in girls.

Precocious puberty due to increased production of human gonadtrophic hormone without a tumor in the region of the pituitary occurs quite frequently. Most cases are described as idiopathic, but some are familial. These cases can be detected by tests for PGF in urine; its detection in the blood is more difficult. Treatment is not indicated because the condition is physiological. A few cases are due to a tumor in the region of the pituitary, but rarely in it. Most such children do not live for more than a few years after surgical and/or radiation therapy for tumor.

Retarded growth with or without obesity, genital infantilism (Frohlich, Neurath-Cushing, and Levi-Lorain syndromes), and secondary hypothyroidism (which is not as profound as the primary form) are diagnostic of hypopituitarism. Craniopharyngioma as a cause is not common. Tumor should be kept in mind

in all cases of suspected hypopituitarism for occasionally these are curable even after partial removal. Epiphyseal age is retarded usually by two or more years, and thorough clinical diagnosis includes tests for adrenocorticotropic (ACTH), thyrotropic (TSH), and gonadotropic anterior pituitary (PGH) hormones. By measuring urinary excretion of 17-ketosteroids and hydrocortisone (compound F) before and after injection of adequate amounts of ACTH, and finding them increased more than threefold after the ACTH test, one can suspect a deficiency of ACTH production. By measuring I^{131} thyroid uptake before and after adequate doses of TSH, and finding more than a twofold increase of I^{131} by the thyroid after TSH one can suspect an anterior pituitary deficiency of TSH production. The diagnostic dose of I^{131} for children can be as low as 1 to 2 μc of I^{131} before TSH, and 2 to 4 μc after TSH, assuming efficient detecting instruments. The body radiation from such doses of I^{131} is very low and is less than that from some radiologic examinations. If a test with I^{131} is indicated for diagnosis, it is justifiable. Pituitary gonadotropin urinary excretion measurement of children below 8 or 10 years of age is normally so low (below 2.5 mouse units per 24 hours) that it is not helpful in the problem of genital infantilism. Physical examination of gonadal status at this age is also not very helpful in diagnosis. Tests with ACTH, TSH, and PGH at best are still gross and difficult to do expertly. Other laboratory tests of thyroid deficiency—blood PBI, cholesterol, BMR—are helpful if done reliably.

Diabetes Insipidus.—Is most often due to posterior (neurohypophyseal) pituitary deficiency in secretion of antidiuretic hormone (ADH) which is probably produced in the hypothalamus and stored in the gland. Lesions of the hypothalamic-neurophypophyseal tract may be more often a cause of diabetes than lesions within the gland. If the anterior as well as the posterior pituitary lobes are destroyed, so that thyroid and adrenal insufficiency are present, diabetes insipidius may not result. Treatment with adrenal and thyroid hormone may bring out diuretic symptoms.

When the diabetes is due to an organic lesion in the hypothalamic-hypophyseal area, neurologic and other pituitary deficiency symptoms usually appear—dwarfism, obesity, and hypogonadism are the more common. Polyuria and polydipsia as the only manifestation (unihormonal deficiency of pitressin) is rare; however, it can be inherited. Diabetes due to the inability of renal tubules to react to pitressin so that water is not reabsorbed is termed nephrogenic diabetes insipidus. This is another inherited type and is rare. Newborns in whom this occurs are termed "water babies," and often have accompanying dwarfism and mental retardation.

Psychogenic polydipsia is not due to lack of pitressin and is not too rare in nervous children. If the urine has a specific gravity over 1.012 when water is withheld until thirst is uncomfortable, true diabetes insipidus can usually be ruled out. In doubtful cases, a more quantitative test, such as the Carter and Robbins modification of the Hickey-Hare test, can be used. This test depends on the known ability of hydrated normal persons to increase osmotic pressure of plasma, which causes an increased production of pitressin and thereby a reduced volume of urine.

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A practical treatment for cooperative children who can medicate themselves is powdered pitressin (snuff) insufflated into the nose in 10 to 20 mg. doses (10 to 20 pressor units) with the patient reclining so that the head is 30 degrees below the body. The frequency of the dose should be regulated for minimum interruption of sleep. If the last dose is given at 9 P.M. this will often be accomplished. Two to four doses in 24 hours are usually required. This approach is advantageous even in infants. For intranasal administration, a 7.5 per cent saline solution (pH 4.5) is satisfactory as a spray or in drop form. When intranasal powder is too irritating one resorts to the intramuscular injection of pitressin tannate in oil (5 pressor units per c.c.), starting with 0.2 c.c. every 24 hours. This is effective for 24 to 72 hours. Children over 8 years of age can be taught to inject themselves. Dosage of all types of pitressin varies for different patients and is determined by trial. For pitressin-resistant diabetes, frequent and large amounts of fluid are imperative.

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THYROID

Hypothyroidism is the most common type of thyroid imbalance, and has several variants: congenital, goitrous, and acquired. The cause of the most common congenital variety (athyreosis or hypoplasia) is still unknown. A recent and surprising development is the finding of antibodies to the thyroid in the blood due to autoimmunization,[1] which presumably arise in the mother from Hashimoto's thyroiditis before or during pregnancy. Thyroiditis can be latent and not known from past history. The inflammatory reaction in the thyroid releases thyroglobulin into the blood which, acting as an antigen, stimulates antibody production in extrathyroidal tissues. The antigen can cross the placenta and set up a similar antigen antibody reaction in the fetus, thereby restraining normal thyroid development. Not all of these babies have detectable antibodies, whether tested for by agglutination, complement fixation, or precipitins. Occasionally they are detected years later in mother and child. The mother may not be hypothyroid during pregnancy, and all hypothyroid mothers do not necessarily have hypothyroid infants.

It is remotely possible that the fetus in utero could develop thyroiditis and antibodies, independently, in a mother with a normal thyroid. There are probably other as yet unknown causes for infantile hypothyroidism beside such an antigen antibody mechanism. Iodine lack, now rare in the United States, may be one other cause.

The clinical picture and laboratory evidence of all types of hypothyroidism do not reveal all of the classical signs or symptoms; even the congenital variety is usually slow in its genesis. Possibly only 10 per cent of maternal thyroid hormone traverses the placenta and medicates the fetus. If the fetus has at least some thyroid gland function it also medicates itself. This effect usually lasts from 2 to 6 weeks or even 3 to 4 months beyond birth, or until the maternal prenatal medication has been catabolized and the baby's sources are not equal to the demands of normal growth and development. Then, the more profound deficiency becomes evident clinically. If the physician keeps hypothyroidism

in mind, the diagnosis can be made early in borderline cases by laboratory aids (low PBI, retarded epiphyseal age); blood cholesterol often is not elevated in infants. The need for early diagnosis is not that the body is quickly reconstructed to normal by thyroid medication but, most important, that mental retardation be corrected or arrested.

Familial goitrous hypothyroidism (autosomal recessive genes) results from the inability to synthesize a normal amount of thyroxine. Enzymatic deficiencies resulting from this congenital defect probably account for those types which are now recognizable. Usually the hypothyroidism appears before the goiter, and occurs in the first 6 months to 1 year of age. The clinical manifestations of deficiency are not always as marked as in athyreosis; goiter may not develop for years after hypothyroidism starts. One of our patients did not develop a goiter for 14 years, another not until 8 years of age. The thyroid tissue shows many areas of hyperplasia, is deficient in colloid, and, occasionally, has areas of atypical malignancy. The goiter is due to excessive TSH production. Potentially normal-reacting tissue must be presumed to be present for hyperplasia to develop. This is probably a compensatory effort to achieve euthyroidism, and would account for the milder clinical hypothyroidism which is sometimes detected.

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At present three enzymatic defects are postulated[2]: in one, inorganic iodine is not organified in the gland to iodinated tyrosines and thyronines; 1.0 to 1.5 Gm. of thiocyanate administration empties the gland of the inorganic iodine and absence of an iodine oxidase in the gland is postulated. In the second, there is a failure of normal coupling of iodotyrosines to form tetraiodothyronine (thyroxine), and this is thought to be due to lack or deficiency in the amount of a specific coupling enzyme. The third defect is the failure to deiodinate idothyrosines and iodothyronines due to deiodinase (dehalogenase) deficiency, Where there may be deficiency of thyroglobulin production or there may be release from the gland of metabolically inactive iodinated protein. Extraurinary excretion of iodotyrosines then robs the body of thyroid hormone precursors. Other types probably will be described to account for other clinical types of goitrous hypothyroidism.

Increased thyroid uptake of I^{131} will be found in practically all of the cases. The hyperplasia demands the additional I^{131}; not all the I^{131} is converted to PBI^{131} and chemical determination of PBI will often show high values. Butanol-extractable iodine (BEI) is definitely in the hypothyroid range, since BEI consists mainly of thyroxine.

Results of therapy are very satisfactory and the goiter usually disappears entirely; however, if it has been present for some years, a residual goiter may persist due to involutionary nodules and fibrous tissue.

Acquired hypothyroidism frequently develops slowly and is difficult to detect, especially if one expects to find many of the classical manifestations. Myxedema, a manifestation of profound deficiency, can be minimal or even localized to parts in the interior of the body so that it is evident only by hoarse voice, swollen stiff joints, failure in school work, slowing of growth, dwarfism, and retardation of epiphyseal development, and it may take 6 to 18—or some-

times 24-months to be certain of the presence of such symptoms. Acquired hypothyroidism is idiopathic and occasionally starts after an illness. One wonders if the thyroid was inherently defective and had little reserve function as in the pancreas of those patients with hereditary diabetes. The reserve of such thyroid glands may be too little to meet stress, or the effort to maintain euthyroidism may be too great.

Treatment of total hypothyroidism requires one or two, and in some cases three, grains of potent thyroid substance daily. A minimum dose produces the maximum benefit in the markedly hypothyroid.

Congenital goiters sometimes occur, even though the mother has not ingested substances (goitrogens, iodides, thiouracil, etc.) which cause short-lived or persistent goiters, and mild hypothyroidism will develop. Usually symptoms recede spontaneously in such patients and euthyroidism ensues. Familial recurrence has been observed and suggests a genetically conditioned metabolic defect.

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Familial hypothyroidism without goiter is a rare type of congenital athyreosis. Ainger and Kelley[3] reported this condition in three siblings, with two other closely related individuals in the family who may have had the same defect. Antibody studies in such families have not been reported.

Simple colloid goiter is disappearing since adequate iodine is available in iodized salt and in foods, and soil in which food is grown in the United States is adequate in iodine except in the Great Lakes area. However, cases have occurred in children who have ingested adequate amounts of iodine, and there may be an additional unknown cause. An inherited inborn metabolic error may be a causative factor, for the writer has found partially iodinated compounds (mono and diiodotyrosines) and unidentified iodinated compounds besides thyroxine in the blood, urine, and feces of such children and adults.

Colloid goiter is possibly a compensatory mechanism in an effort to maintain euthyroidism. Due to the strain on the thyroid it is possible that TSH is increased in production and causes the goiter. The goiter more often diminishes during thyroid than during iodine medication. Thyroid therapy relieves some of the strain on the thyroid and also contains an adequate amount of iodine for normal requirements.* It is still unexplained why the frequency of colloid goiter is greater in girls; girls may need more iodine and thyroid at puberty than boys do.

Hyperthyroidism occurs more often during growth stress, as at puberty, and more commonly in girls (6:1); the latter fact has not been fully explained. The forme fruste is more common than the florid type, is often difficult to diagnose, and seems to be related, at least partly, to excessive TSH production. Iodine deficiency no longer seems to be an important cause. There is often a family history of thyroid disease, usually of hyperthyroidism or simple goiter. Psychogenic factors are often present and are related to the onset and maintenance of the overactivity. Physical features in children who have florid Graves' disease are extra growth in height due to the increased protein anabolism and some suppression of gonadal maturation. The extra growth could be related to

*The normal daily requirement of iodine for a child is between 20 and 2,000 μg. One grain of thyroid extract has 110 μg and 1 drop of Lugol's solution has 8,430 μg of elemental iodine.

increased somatotropic production in the pituitary along with TSH production, recalling that pituitary disturbances are usually multi- rather than unihormonal. This disease often runs in cycles of relapses and remissions; if untreated it lasts for years, occasionally "burning out" the gland and resulting in hypothyroidism.

In the forme fruste and in cases with only moderate toxicity, medical care with propylthiouracil, sedation if indicated, and some restricted activity are usually sufficient to arrest the disease. For mild cases 100 to 300 mg. daily of propylthiouracil are average doses; for florid toxicity amounts of propylthiouracil such as 300 to 500 mg. for smaller children and even 1,000 mg. daily for larger children are necessary. The patient should be prepared for an operation when the cycle is in remission. If an operation is not performed the chances are great (50 per cent) that relapse will occur. Adequate removal implies leaving 2 to 4 grams of thyroid gland, and is rarely attended by permanent hypothyroidism, hypoparathyroidism, or failure to mature. Mortality rates for such an operation should not exceed 0.5 per cent.

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PARATHYROID

Chronic hyperparathyroidism is primarily or secondary in occurrence; the latter is more common but both are rare. Primary hyperparathyroidism (idiopathic) due to adenoma is quite rare in childhood. The findings in both types are increased blood calcium and alkaline phosphatase; increased urinary excretion of phosphorus and calcium; tender painful bones, osteoporosis, cystic bones which fracture easily, lack of calcification, simulating rickets at growing ends of bones; metastatic calcification in soft tissues around joints, ligaments and cartilages, in basal ganglia, in kidney as stones, and in conjuctiva and cornea.

Secondary hyperparathyroidism occurs in chronic renal insufficiency associated with metabolic acidosis and retention of phosphate, as in some cases of chronic glomerular nephritis and pyelonephritis from urinary tract defects. Blood calcium is lowered secondary to phosphate retention and the parathyroid glands enlarge in an effort to compensate. The glands also enlarge secondarily after poor calcium absorption in steatorrhea and refractory rickets. The hypocalcemia of the various states leads to osteoporosis.

Primary hyperparathyroidism can eventually damage the kidneys so that blood phosphorus increases, blood calcium decreases, and phosphorus excretion diminishes. After some time the skeletal findings can be confused with osteitis fibrosa cystica which results from renal insufficiency. When renal calculi or decalcification appear without obvious cause, the possibility of hyperparathyroidism should be investigated. The primary type is treated by removal of the adenoma of the parathyroid, or by subtotal parathyroidectomy for hyperplasia. Chronic tetany may result after this.

Chronic hypoparathyroidism can occur when the glands have been removed during thyroidectomy or have been traumatized or destroyed by hemorrhage or prolonged edema.

Idiopathic chronic congenital hypoparathyroidism is very uncommon. Usually the symptoms start in early infancy—occasionally in a previously normal child. Addison's disease has occurred in some of these cases. Monoliasis has been

present in some of these cases, but etiological relationship of such infection to the parathyroid and adrenal disturbances is questionable. A combination of tatanic convulsions; trophic changes in teeth (faulty dentine, pitted enamel), skin, hair, and nails; cataracts; and osteoporosis strongly indicate idiopathic hypoparathyroidism. Hypocalcemia is primary and hyperphosphatemia is secondary to it. The serum phosphatase is low or normal. There is no calcuria.

A diagnosis of hypoparathyroidism is confirmed by correction of chemical abnormality by parathormone, dihydrotachysterol, or, preferably, by heavy doses of vitamin D (400,000 units daily at the start; 50,000 to 100,000 units when blood calcium rises to 8 or 9 mg. per cent. Parathormone administration is not practical in the chronic state after a few weeks, since patients become refractory. Thyroid medication may be helpful when control is difficult. If the patient has active tetany, calcium gluconate intravenously or calcium chloride orally should be given; when the tetany disappears vitamin D can be started and calcium salts discontinued gradually.

Pseudohypoparathyroidism is a rare familial disorder of unknown etiology wherein the end organs—particularly the kidney—do not respond to the patient's parathormone. Phosphate diuresis does not occur after administration of parathormone. In addition to clinical and chemical findings of the idiopathic type, the patients are short, stocky, and have a round face. There is a tendency to brachydactylia; the index finger may be the longest of all fingers. There may be dimples instead of kunckles on the lateral fingers Along with osteoporosis, calcifications occur in basal ganglia and subcutaneous tissues. Therapy consists in administration of vitamin D.

ADRENAL

Disease of the adrenal cortex is the cause of more chronic endocrinopathies than is disease of the medulla. Chronic adrenal insufficiency of the adult type (primary, idiopathic Addison's disease) is rare in children; that caused by tuberculosis still occurs more often than the primary type. The "idiopathic" variety can occur after hemorrhage during flexing maneuvers for breech delivery—calcifications are noted in x-ray films which simulate tuberculosis, and the clinical picure is similar to that of the adult variety. Crises occur readily during stress or illness—salt loss is one of the principal problems. When salt equilibrium has been attained, fluorhydrocortisone orally, 0.05 to 1.0 mg. daily, or desoxycorticosterone trimethylacetate (DCTA) 10 to 25 mg. once monthly intramuscularly can be used for long-term therapy. Additional sodium chloride (3 to 6 Gm. daily) can be given if control of salt loss is difficult.

Hyperadrenocorticism.—Adrenogenital and Cushing's syndrome occur not too rarely in children, while aldosteronism and feminizing adrenal tumors are quite rare.

The adrenogenital syndrome is characterized by excessive masculinization, increased protein anabolism with extra growth in height and muscular development due to excessive production of adrenal androgen. This syndrome may be due to hyperplasia or tumor of the adrenal cortex. The clinical findings vary with sex and age at onset.

The congenital form in girls (pseudohermaphroditism) is accompanied by bilateral adrenal hyperplasia. Virilization which starts postnatally and before puberty may be due to tumor, although hyperplasia can be the cause. In males (macrogenitosomia praecox), the appearance of pubic hair and genital growth may be delayed two to three years, though hyperplasia may have been present in utero. After puberty the syndrome may be due either to hyperplasia or tumor. About one quarter of these patients are born with disturbances of sodium loss, potassium elevation, and water regulation (Addisonlike complex) which may cause early death from dehydration, circulatory collapse or cardiac arrest because of hyperkalemia. Occasional patients have hypertension; a few have hypoglycemia due to deficiency of glycogenetic hormone (compound S; 11-desoxy-17-hydrocorticosterone).

The adrenogenital syndrome is due to an inherited deficiency of some enzymes in the adrenal cortex which chemically control normal formation of its hormones; it is found frequently in siblings, probably as a homozygous recessive trait. Bongiovanni and co-workers[4] hypothecate a deficiency of 21-hydroxylase for the normal hydroxylation of 17-hydroxyprogesterone to form compounds F and B. Hydrocortisone production is thereby deficient, and is accompanied by overproduction of pregnanetriol in the urine, which is a metabolite of 17-hydroxyprogesterone (Table I). In occasional patients with hypertension there is a different enzymetic defect in hydrocortisone production—a deficiency of 11-hydroxylase[5]—where there is increased production of DOC and compound S. In the hypertensive form, hydrocortisone production is kept normal by normal ACTH stimulation; DOC production is related to the hypertension, though edema and electrolyte disturbances are absent. In all forms of the adrenogenital syndrome, extra ACTH stimulation leads to cortical hyperplasia but this does not fully correct the inborn enzymatic defect; increased cortical androgen production results in virilization.

Treatment of Adrenogenital Syndrome.—Cortisone, the preferred hormone for treatment, suppresses the production of ACTH and, thereby, the biologically active cortical androgens. Hydrocortisone has been used for its cortisonelike action. For electrolyte regulation, fluorhydrocortisone or cortisone acetate (DCA) are the preferred hormones. Various preparations of cortisone and hydrocortisone are available: tablets for oral ingestion; solutions for injection for rapid or for sustained action, and fluorinated forms for marked sodium retention if necessary. Dosages given here are for hydrocortisone since it is used most often because of lack of accumulated experience with other hormone preparations. Large doses are given at the start of therapy for rapid control; with the decrease of urinary ketosteroid excretion as the guide (about five days of therapy) it is possible to determine the minimum maintenance dose. Pregnanetriol excretion disappears under therapy. The initial suppression is obtained preferably by intramuscular rather than oral hydrocortisone. For older children, the total dose for rapid control is about 50 to 100 mg. intramuscularly daily; for infants, 25 mg. daily, divided into 3 to 4 doses. The maintenance doses can be given intramuscularly every 3 to 5 days—for older children 70 to 100 mg. (about 25 mg. daily); for infants, 25 mg. every 3 days or 37.5 mg. every 4 days (about 8 and 9 mg. daily

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respectively). For prolonged maintenance, orally administered doses are used; adequate doses for older children are 50 to 70 mg. daily in 3 to 4 divided doses; for young infants, 5 mg. 4 times a day. Sudden withdrawal of therapy is to be avoided, since the adrenal cannot respond quickly. Extra doses must be given pre-and postoperatively: 50 to 100 mg. intramuscularly daily for 2 or 3 days, before and after surgery. During the postoperative period the injected dose is tapered while oral medication is added. For acute emergencies, hydrocortisone given intravenously or orally has a more rapid effect than when given intramuscularly. Occasionally hydrocortisone therapy has been stopped for 3 or 4 months without mishap; 17-ketosteroid excretion rises slowly, virilization ensues and epiphyseal age then advances.

The action of hydrocortisone is due to its inhibiting effect on ACTH production. When this occurs adrenal androgen production and virilization are diminished. When the production of adrenal androgens and estrogens (antagonized by androgens) is brought down to normal, pituitary gonadotropic production is probably normal and normal gonadal and adolescent sexual development can occur in the prepubertal patient.

Treatment for Electrolyte Loss.—if the patient can tolerate oral sodium chloride, 4 to 8 gm. daily should be given; if the patient is vomiting, parenteral administration of salt solution is necessary. Hydrocortisone should be given early, plus DCA, 1 mg. daily, or fluorhydrocortisone 0.05 to 0.1 mg. daily in order to reduce 17-ketosteroid production and to correct salt imbalance; some prefer to implant DCA pellets after stabilization has been attained. Maintenance of dietary salt supplementation and cortisone must be continued; DCA implants or dosage in the congenital type may not be necessary after 9 to 12 months of therapy for infants. With hydrocortisone therapy, the tendency to salt loss diminishes with time. The families of patients must be cautioned about the critical dangers of illness, and extra hydrocortisone for oral use should always be available at home. Fluorohydrocortisone is not advisable in all children with this disorder.

The decision is difficult as to which sex the child should be reared in. Sex chromatin patterns of buccal mucosa indicate the type of gonad. Girls with the disorder should be raised as females and hydrocortisone should be started as soon as the diagnosis is made. If the clitoris is conspicuous some authorities advise amputation between the ages of 2 to 5 years and fusion of labioscrotal folds corrected to effect a normal vaginal introitus; others think that amputation should be done just before puberty. When hydrocortisone is started in older females who are reared as girls, the same operations should be performed. Female pseudohermaphrodites raised as males up to the age of 3 or 4 years should not be changed into females because of the psychological hazard involved. If cortisone is used to prevent early epiphyseal fusion in dwarfism, oophorectomy should be employed to stop breast development.

Males who have macrogenitosomia praecox should be given hydrocortisone to prevent dwarfism and too early virilization. No operation is necessary unless a tumor is demonstrated by x-ray localization, with the use of oxygen injected presacrally, permitting the oxygen to drift upward and outline the adrenal tumor.

TABLE I. TESTS OF CERTAIN ADRENAL CORTICAL STATES*
(20 Units ACTH/1,000 c.c. 5% D–W I. V. for 8 Hours)

NORMAL AGE—YEARS	ACTH STRESS TEST				SUPPRESSION TEST
	URINE 17-KETOSTEROIDS		URINE 17-OHCS		FOR EACH 1 MG. 17-OHCS IN URINE, GIVE 1 MG. PREDNISOLONE, EVERY SIX HOURS, FOUR TIMES A DAY FOR 3 DAYS.
	BEFORE	AFTER	BEFORE	AFTER	
0– 2 2– 6 6–10 10–14	1– 2 2– 4 2– 6 4–10	1-2x increase	2– 4 3– 6 4– 8 4–10	3-5x increase	Up to 50% decrease
Congenital bilateral hyperplasia	15 Pregnanetriol 1	1-5x or more increase	Increase	Up to 5x increase	17 KS should be reduced 50%, failing which one suspects adenoma, cancer, Leydig or interstitial cell tumor or other ovarian cause
Benign Adenoma	15	Marked increase	Slight increase	5-7x increase	No suppression generally
Adenocarcinoma	High; occasionally 50	No increase	Marked increase	No increase	No suppression

*Data of P. H. Forsham, M.D., and V. C. DiRaimondo, M.D., University of California School of Medicine, San Francisco. All figures are mg./24 hours; 50% variation of values in different laboratories. There are occasional exceptions to these values for the various pathologies.

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The effect of hydrocortisone on sexual development of girls depends on the somatic development previously attained. In infants, maturity can be postponed until normal age. In the older girls (3 to 8 years) a gradual normal maturity occurs during the next few years; in girls beyond 8 or 10 years, normal female development occurs rapidly. Menses can occur and virilization is checked. Pregnancies are uncommon and often result in miscarriage, although there are several recorded instances of the birth of normal infants to such patients.

The effects of hydrocortisone on sexual development of boys depends on the development attained before therapy. Normal masculinization, including spermatogenesis, usually occurs during adequate therapy.

Effects of Hydrocortisone on Somatic Growth and Development.—The untreated case develops dwarfism because of premature closure of epiphyses; this can occur in treated patients when epiphyseal development was previously considerably advanced. If adequate amounts of hydrocortisone are started early in life and dosage properly adjusted, normal growth and development can be expected; hypertension and pigmentation can disappear. Excessive cortisone can retard growth.

Cushing's Syndrome.—Most of the cases in children have adrenal tumors, which are frequently malignant. There does not seem to be proven abnormality of synthesis of adrenal hormones. Stimulation by exogenous ACTH may be causing production of extra cortisone but usually not of 17-ketosteroids (Table I). Extra production of the following adrenal hormones is postulated: 1. Glucogenetic (cortisone), leading to extra formation of carbohydrate from amino acids and a decrease in protein anabolism, resulting in weakness, dwarfism, obesity, fatigue, striae, ecchymosis, ease of bruising, osteoporosis with or without blood sugar alteration. 2. Androgens, leading to some—but not marked—hirsutism, seborrhea, acne, and sometimes clitoral hypertrophy. Occasionally, true precocious puberty develops; in girls extra production of estrogens as well as androgens possibly occurs in some cases. 3. Electrolyte-controlling hormones (aldosterone), resulting in hypertension, plethora, and electrolyte changes. Though the electrolytes are not usually changed in the blood, there may be intracellular changes; urinary and plasma cortisone are variably increased; 17-ketosteroids are still more variable.

A mixed picture between the Cushing and the adrenogenital syndrome is frequently found, particularly when a tumor is present.

The removal of the tumor offers the best possibility for cure. Exploration may be attempted, since clinical proof of its presence may be difficult. Intense supportive therapy with sodium chloride and hydrocortisone is necessary pre- and postoperatively since the contralateral gland often has disuse atrophy. If only hyperplasia is found, resection of parts of each gland or total bilateral adrenalectomy can be performed. The latter operation requires lifelong replacement therapy with hydrocortisone and DCA. Cortisone suppression of adrenal hyperactivity is not effective in Cushing's syndrome. Radiation of the pituitary for control of ACTH production helps only occasionally but can be tried before bilateral adrenalectomy. Androgen therapy controls the reduced protein anabolism somewhat and is helpful for the correction of osteoporosis.

Aldosteronism is a rare and usually unihormonal deficiency in children; it occurs more often as a secondary manifestation, as in nephrosis. There is recent evidence by Farrell[6] that aldosterone secretion results from an adrenal glomerulotropic hormone (GTH) produced primarily in the pineal complex of the posterior diencephalon. GTH production is directly but slightly increased by ACTH, by definitely decreased body fluid volume, and by hyperkalemia. Hypokalemia and hypernatremia explain the intermittent muscle weakness and paralysis. Alkalosis develops easily and other findings are hypertension, muscle spasms, attacks of tetany, large volumes of urine with low specific activity, and protein uria. Tumors are usually the cause of this syndrome and their removal results in cure unless metastases are present.

Feminizing tumor of the adrenal is rare; there are 12 reported male cases but only one in a child. Adrenal estrogen production is high and is measurable in blood and urine. Occasionally androgen production is increased but virilization is minimal. The feminization is principally manifested as gynecomastia and oligospermia. Removal of the tumor is curative unless malignant metastases occur, which is common.

The only chronic endocrinopathy of the adrenal medulla is the pheochromocytoma. Relatively few cases are on record of epinephrine and norepinephrine having been produced. Hypertension, occasionally intermittent, is the most frequent finding.

GONADS

Chronic primary gonadal endocrinopathies will be discussed briefly. Adolescence and puberty can be precocious or delayed due to normal physiologic variations; about 9 of 10 of these common problems turn out to be due to this. However, each case merits thorough clinical evaluation and examination by appropriate laboratory tests. Familial tendencies should be studied, especially the onset of secondary gonadal characteristics and menarche. In boys accurate history of maturity in paternal forebearers and fraternal siblings is not too accurate, for spermatogenesis—the counterpart of menarche—does not reveal itself in obvious fashion. Disturbed height growth usually accompanies problems of maturity and requires the same inquiry into family tendency—for several generations if possible. Over 75 per cent of girls mature (menarche) normally between 9 and 16 years; in boys, full maturity (spermatogenesis) is probably attained between 9 and 18 years. Assurance that there is no pathologic cause and that the findings are within the range of normal expectancy, will greatly allay the concern of the family and obviate the disadvantages of endocrine therapy with its costs and undesirable reactions—particularly virilization in girls or breast growth in boys. It is well, however, to reappraise such problems at least every 3 to 6 months in the ensuing several years in order not to miss any pathologic cause.

Neurogenic origins occur in some cases of infantilism (more commonly) and sexual precocity. The origin is thought to be in the hypothalamus though nerve pathways and influences on the anterior pituitary have been demonstrated. A few of the pathologic lesions are tumors in the proximity of the anterior pitui-

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tary (floor of the third ventricle, optic chiasm, and tuber cinereum); some are due to maldevelopment in utero (without known cause), during birth, or shortly thereafter; still others occur after encephalitis, meningitis, head injury, and hemorrhage. Other symptoms of hypothalamic origin which may be present are: somnolence, temperature irregularities, and diabetes insipidus. Clinical findings arising outside of the hypopituitary-hypothalamic area may be also present, and include: cranial nerve palsies, behavior problems, mental retardation, and enlarged cerebral ventricles.

Definitions of hermaphroditism, pseudohermaphroditism, and intersex should be mentioned. True hermaphroditism is most rare and consists of the presence of testicular and ovarian tissue in the same individual; both tissues may be functionally active but usually various degrees of inactivity are present. There may be many variations in the male and female differentiation of the external and internal genitalis. Pseudohermaphroditism exists when the gonads of only one sex are present with abnormalities of the external genitalis or secondary sex characteristics. An individual with intersex or an intergrade intersex shows characteristics between the typical male and female condition. Determination of the sex chromatin pattern in a cell nucleus[7] may be helpful but is at times confusing. Some surprising developments are the so-called externally female young children with gonadal dysgenesis, in whom male sex chromatin is found in 75 per cent of the cases. In girls with testicular feminization (male pseudohermaphroditism) in whom the chromatin pattern is male the testicular gonad probably secretes estrogens. In female pseudohermaphroditism with virilization due to adrenal cortical causes the patterns are female (positive).

The sex chromatin pattern does not necessarily determine function of the gonad during intrauterine life. The fetal testis secretes a product which inhibits fetal female development in the Mullerian system and favors the development of male structures by the Wolffian system. The pattern can be studied in any cell in the body but is done more practically on buccal mucosal cells. With improvement in the study of sex chromosome patterns, results may be more helpful and less confusing.

OVARY

Hypofunction due to ovarian dysgenesis or to aplasia is more common than realized, and may account for over 35 per cent of cases of sex infantilism in "girls" (about four times more common in girls than in boys). Characteristics of ovarian dysgenesis are moderately reduced growth (50 to 58 inches adult height), slightly retarded epiphyseal age (but not as much as height age), mature facies for age, and a resemblance to other cases of dysgenesis, with underdevelopment of jaw and mandible, wide neck (pterygium coli of Turner)[8] low hair line in about one half of cases, increased carrying angles at elbows, wide thorax ("shield chest"), marked diminution in development of secondary ovarian characteristics (lack of estrogen); anomalies in skeleton (fused or hemivertebrae and ribs), skin (moles, freckles, telangectasia), vascular system (coarctation, unexplained hypertension), and eye (muscle imbalance). In a few cases the underdevelopment of external genitalis is accompanied by an enlarged clitoris. Gordan and co-workers[9] showed

that this masculinization was attended by nests of Leydig cells and rete tubules in the ovarian streak, and a greatly increased excretion of 17-ketosteroids. Afflicted infants are often born with edema of dorsa of hands and feet, which may persist for years. Pathologically the ovary is deficient in medullary elements, and the cortical elements (primordial ova) are absent or very immature. The sex chromatin pattern is male in 75 per cent or more of cases. In early embryonic life when elements of both testes and ovaries are present and before sex differentiation occurs, castration invariably leads to female differentiation.[10]

Increased FSH excretion is diagnostic; it is often unbelievably high—300 to 400 mouse units daily—but elevation in young patients occurs irregularly. The increased FSH may be due to lack of ovarian estrogen which normally keeps production of FSH within normal ranges. The anomalies of development and the stunted growth cannot be explained on an endocrine basis. Removal of ovaries before adolescence leads to increased stature and eunuchoid proportions.

Embryological maldevelopment seems to explain ovarian dysgenesis. The Bonnevie-Ullrich syndrome seems to be a variant of the Turner type; both have many common findings. Differentiation involves consideration of primary pituitary hypogonadism with stunted growth. Until Turner[8] described ovarian dysgenesis (though in 1938 he did not have knowledge of the maldevelopment of the ovary) most cases were considered to be of pituitary origin. In pituitary hypogonadism there are varying degrees of lack of FSH and, therefore, of hypogonadism. Usually the daily production of FSH is much below normal (2.5 to 5 mouse units) and it is not greatly increased as in ovarian dysgenesis. Androgenic production by the adrenal may be normal but is usually reduced, and boys may have persistently small testes or cryptorchidism. Dwarfism and retardation of epiphyseal development is more marked in the hypopituitary cases. Occasionally, amenorrhea and azospermia are permanently present in pituitary cases; in some hypopituitary girls FSH production may not be markedly low, and the pituitary luteinizing factor may never be produced. Occasionally also there may be only a temporary production failure, as in anorexia nervosa. The absence or a defect of the gonads is quickly diagnosed by finding a high urinary excretion of pituitary gonadotropic hormone.

Treatment of ovarian dysgenesis is by replacement therapy with estrogens which feminize the girl. The patient and family probably should not be informed about the finding of male sex chromatin. Estrogen therapy is preferably started at the normal age of puberty—13 or 14 years. With stilbestrol or diethylstilbestrol—1 mg. orally (occasionally 5 mg. daily are necessary) daily for about 21 days and none for the next 7 days in order to simulate the normal cyclic production of estrogens—rapid feminization develops, including pigmentation of nipples. Usually after 3 to 6 months uterine bleeding starts. If nausea and vomiting appear, intramuscular injections of hexestrol or ethinyl estradiol can be substituted and orally administered stilbestrol can be repeated later. Anhydrohydroxyprogesterone (a progestin) can be given with stilbestrol during the third week to simulate ovarian luteal activity. If estrogens are given before the age of 13 or 14 years it is possible to accelerate epiphyseal closure and stimulate

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height growth. We have tried to stimulate height by anabolic hormones (Nilevar, Halotestin and various pituitary growth hormones) before inducing puberty but the ultimate results are usually not more than a 5 cm. increase. This is borrowing height from the future and is not an addition to the ultimate expected height. However, some patients appreciate such growth at this age because it gives them a sense of "belonging" with their contemporaries.

In males, it is questionable if the counterpart of Turner's syndrome occurs. We see a number of dwarfed males with webbed necks, some degree of gonadal hypoplasia, male sex chromatin, and some questionable elevation of FSH.

Removal, destructive disease (mumps, pelvic tuberculosis), or hemorrhagic infarction of gonads before puberty results in eunuchism, with disproportionate tallness and failure of full development of secondary sex characteristics. The differentiation from pituitary origin is by the measurement of PGF excretion (absent or low in cases of pituitary origin, and supernormal in those of gonadal origin).

Treatment of males with hypopituitary sexual infantilism can be tried with gonadotropins though it is often ineffective and disagreeable, for injections must be given for 6 to 12 weeks. Since there is no effective pituitary preparation, chorionic gonadotropin is used in doses of 1,000 rat units three times a week. Substitution therapy with androgens orally is more practical. With 20 to 30 mg. methyltestosterone, taken daily for as long as secondary characteristics develop and epiphyses are still open, height increases of 7 to 9 inches may be attained. Spermatogenesis occurs only occasionally.

Girls can be treated with combinations of estrogens, progestins, and androgens. Sexual hair is frequently not present; estrogen alone or androgen with estrogen will often bring out normal hirsutism. Virilization should not be allowed to develop; the dose should be reduced or the androgen temporarily discontinued.

Primary pathologic hyperfunction of the gonads is rare; the palpation of a tumor in a gonad is diagnostic. In a girl a good rectal examination is advisable; occasionally, laparotomy is necessary for localization and pathological diagnosis. Some of the causes in girls, in order of frequency, are: granulosa cell tumor, chorionepithelioma, teratoma, and luteoma; in boys, the neoplasm is an interstitial cell tumor.

REFERENCES:

1. Roitt, I. M., Doniach, D., Campbell, P. N., and Hudson, R. V.: Autoantibodies in Hashimoto's Disease (Lymphadenoid Goitre), Lancet **2**:820, 1956.
2. Stanbury, J. B., and Querido, A.: Genetic and Environmental Factors in Cretinism: A Classification, J. Clin. Endocrinol. **16**:1522, 1956.
3. Ainger, L. E., and Kelley, V. C.: Familial Athyreotic Cretinism: Report of 3 Cases, J. Clin. Endocrinol **15**:469, 1955.
4. Bongiovanni, A. M., Aberlein, W. R., and Cara, J.: Studies on the Metabolism of Adrenal Steroids in the Adrenogenital Syndrome, J. Clin. Endocrinol. **14**:409, 1954.
5. Eberlein, W. R., and Bongiovanni, A. M.: Congenital Adrenal Hyperplasia With Hypertension: Unusual Steroid Pattern in Blood and Urine, J. Clin. Endocrinol. **15**:1531, 1955.
6. Farrell, G. L.: Steroidogenic Properties of Extracts of Beef Diencephalon, Endocrinology **65**:29, 1959.
7. Moore, K. L., Graham, M. A., and Barr, M. L.: The Detection of Chromosomal Sex in Hermaphrodites From a Skin Biopsy, Surg. Gynec. & Obst. **96**:641, 1953.

8. Turner, H. H.: A Syndrome of Infantilism, Congenital Webbed Neck, and Cubitus Valgus, Endocrinology **23**:566, 1938.
9. Gordan, G. S., Overstreet, E. W., Traut, H. F., and Winch, G. A.: A Syndrome of Gonadal Dysgenesis: A Variety of Ovarian Agenesis With Andorgenic Manifestations, J. Clin. Endocrinol. **15**:1.
10. Jost, A.: Recherches sur la différenciation sexuelle de l'embryon de lapin, Arch. Anat. Micr. Morph. Exp. **36**:271, 1947.

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NEWER VIRUS DISEASES IN CHILDHOOD

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IN THE past ten years approximately one hundred new viruses have been discovered. This tremendous advance in our knowledge means that the clinician is faced with a major problem of learning about the diseases caused by them. These new viruses are not only numerous but they cause the most prevalent diseases of man. The physician can no longer be content to describe or define these diseases in vague anatomic terms such as tonsillitis, pharyngitis, bronchitis, or "the flu." It is necessary to begin to think etiologically and make every effort to arrive at an etiological diagnosis in order to treat the patient wisely. Many of these agents may cause aseptic meningitis, encephalitis, diarrhea, or acute respiratory disease in its various manifestations from mild inapparent illness to severe pneumonitis and death.

Emphasis will be placed on the *adenoviruses* as well-defined causes of acute pharyngitis, possible laryngitis, and most certainly viral pneumonitis. The influenzas will not be discussed in detail but we shall refer to other *myxoviruses* which cause acute respiratory disease. Certain of the *enteroviruses* will also be discussed particularly those identified with diseases of the meninges, the gastrointestinal tract, and the respiratory passages. Primary atypical pneumonia with positive agglutinins for MG streptococcus and cold hemagglutinins, most probably caused by viruses, will also be discussed very briefly. The syndrome of viral pneumonia is undoubtedly part of the spectrum of many of the newer viruses capable of causing primary disease in the respiratory passages. Atypical pneumonia is not a separate entity but part of the spectrum occurring in a definite but small percentage of individuals who suffer from viral and other nonbacterial respiratory tract infections.

MYXOVIRUS DISEASES

This group of viruses is distinguished by their special affinity for certain mucins, and the major diseases in this group are the influenzas A, B, and C. The parainfluenzas 1, 2, and 3 (originally called hemadsorption viruses) are known to cause acute respiratory disease characterized by croup, acute nasopharyngitis, and pneumonitis. The isolation of these new myxoviruses was accomplished by a technique originally described by Vogel and Shelokov[1] in which

they found that guinea pig red cells were adsorbed onto the monolayer tissue culture which was inoculated with washings from patients with acute respiratory disease. Chanock and associates[2] reported types 1 and 2 hemadsorption viruses as causes of disease in man. The hemadsorption phenomena can be inhibited by specific serum obtained from patients who have recovered. Type 1 hemadsorption virus was isolated first from the patients in a nursery following the outbreak there of an acute febrile disease. The first isolations were made in individual who were described as having acute pharyngitis, bronchiolitis, and pneumonia. Of the 8 patients studied in detail, viruses were isolated from 7. Six of these demonstrated antibody rises by the complement fixation procedure.

Temperature elevations persisted for about 3 days. The patients exhibited cough, and several were described as having fine râles in the chest. There were 3 patients with otitis media. Although the illness was described as mild, many of the patients having rhinorrhea as the chief complaint demonstrated at the same time fever and associated pulmonary involvement.

Hemadsorption type 2 virus was recovered from children with laryngotracheobronchitis or croup. This agent was employed in human volunteer studies by Reichelderfer and co-workers.[3] The agent was found to be infectious for adults, even though many had some previous titer. Thirty-two volunteers ranging in age from 21 to 46 were inoculated with virus from a baby with acute laryngitis. Although 7 of the 32 volunteers developed no titer, the remaining 25 had a demonstrable titer.

The clinical picture presented by the human volunteers was that of an acute respiratory illness which was mild and followed by recovery. Symptoms were described as "coldlike" with coughing and sneezing, although there were some complaints of sore throat, chest pain, and hoarseness. The main physical finding was a reddened edematous pharynx at the onset associated with rhinorrhea and inflamed nasal membranes. Fevers were of low grade and the white blood counts were normal. An epidemic occurred in the institution which appeared 8 days following the first cases in the volunteer study. Type 2 virus was recovered from 8 of the secondary cases which were again described as being acute respiratory illness of a mild nature. A third myxovirus was described by Chanock in 1956,[4] isolated originally from infants with croup and unrelated to either type 1 or 2 hemadsorption agent. This "croup associated" agent is now known as parainfluenza 2. The adenoviruses as well as the influenza viruses were ruled out as causes of the epidemic.

ADENOVIRUS DISEASES

There are more than 20 distinct types of adenoviruses which have been isolated from human beings during the past 5 or 6 years. All of the first five types cause disease characterized chiefly by acute febrile pharyngitis. A distinct syndrome called pharyngoconjunctival fever was described in the early reports as being primarily due to type 3 adenovirus. However, a large variety of additional types including 7a and 14, as well as 1, 2, 5, and 6 are now identified with the pharyngoconjunctival fever syndrome.

A wide clinical spectrum of illness is caused by the adenoviruses. Hilleman[5] showed that approximately 50 per cent of military recruits infected by type 4 adenovirus have no apparent illness. About 20 per cent are sick enough to be admitted to the hospital with acute respiratory disease and 15 per cent of these develop virus pneumonia. The epidemic form of disease known as acute respiratory disease (ARD) was first defined etiologically by Hilleman and Werner in 1954.[6]

Apart from the influenzas, the adenovirus infections represent a well-defined entity caused by viruses and designated acute respiratory disease. In addition to the three clinical syndromes just referred to, acute pharyngitis, pharyngoconjunctival fever, and acute respiratory disease, several additional clinical entities caused by these viruses have been recognized. Pneumonitis in infants has been identified as being due to types 7a, 1, and 3 and pneumonia in adults is related primarily to types 4, 7, and 3. Huebner[7] delineates acute follicular conjunctivitis as due to many of these same types, including 3 and 7a as the most common, but types 2, 6, 9, and 10 are also identified with this clinical syndrome. The clinical picture is known as epidemic keratoconjunctivitis (EKC), the classic disease being caused by type 8 adenovirus. Types 3 and 7a also caused mild but definite cases of keratoconjunctivitis (Table I).

The adenovirus infections have been reported from many countries in the world in the short period of the past 6 years. Newborn infants are known to have demonstrable complement-fixing and neutralizing titers as a result of the passive transfer of antibodies from their mothers. During the preschool age, children

TABLE I. CLINICAL SYNDROMES DUE TO ADENOVIRUSES

DISEASE	ADENOVIRUS TYPES IMPLICATED		COMMENTS
	MOST COMMON	LESS COMMON	
Acute febrile pharyngitis	1, 2, 3, 5		High endemic rates of types 1, 2, and 5 in infants; type 3, epidemic; more common during cold months; similar to pharyngoconjunctival fever but without conjunctivitis
Pharyngoconjunctival fever (PCF)	3, 7a, 14	1, 2, 5, 6	Epidemic in children, sporadic in adults; summer epidemics frequently associated with swimming
Acute respiratory disease (ARD)	4, 7	3, 14	Epidemic in military recruits, sporadic in civilian adults; type 4 and 7 infections rare in children
Virus pneumonia			
In infants	7a	1, 3	Rare; occurs in hospital nurseries; may be fatal; similar to Goodpasture's inclusion body pneumonitis
In adults	4, 7	3	Associated chiefly with ARD; cold agglutinins not developed
Acute follicular conjunctivitis	3, 7a	2, 6, 9, 10	Sporadic; adults chiefly affected
Epidemic keratoconjunctivitis (EKC)	8 (classic cases)	3, 7a	Epidemic; adults chiefly affected; common in Japan, rare in United States

acquire antibodies against various types, but particularly types 1 and 2. Nearly all adults have some antibody for at least one type of adenovirus. Although adenovirus infections are known to be highly significant in military recruits, causing a disease clinically known as ARD, the question of their incidence in the civilian population is not as yet clearly defined.

Jordan[8] in 1957 made only 10 isolations in over 500 individuals with acute respiratory disease, and the serologic studies also failed to reveal more than 5 per cent positive. Evans[9] reported 161 acute respiratory diseases per 1,000 students and found that they were the commonest illnesses in the health service at the University of Wisconsin. However, the incidence of adenovirus infection remained low and was similar to that found in the Cleveland family studies (1 to 5 per cent). Loosli and associates[10] found adenovirus infections to be the major cause of acute respiratory disease in military inductees. The disease has been found to be common in summer camps and in certain susceptible households. Epidemics have been associated with swimming pools and several summer epidemics have been reported in children. Although the over-all incidence in acute respiratory disease is low, epidemics with a high attack rate may frequently be caused by these agents in both military and civilian populations.

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All of the adenoviruses grow readily in tissue culture of human and monkey cells where they cause a distinct destruction of tissue referred to as cytopathogenesis. They will not infect ordinary laboratory animals and are resistant to antibiotics. There is a common complement-fixing antigen in all types. The adenoviruses are approximately the size of the influenza viruses and are estimated to be from 80 to 120 mm. in diameter. They are readily isolated from the intestinal tract and have been found in mesenteric lymph nodes, but syndromes associated with their presence in the gastrointestinal tract are not clearly defined.

The clinical features will be discussed together inasmuch as there is now known to be a great deal of overlap in most of the syndromes caused by these agents. In general, these diseases are characterized by follicular conjunctivitis, acute pharyngitis, and fever. Fever persists up to 4 or 5 days with patients complaining of sore throat in about 75 per cent of the cases. The same percentage present evidence of inflammation of the bulbar and palpebral conjunctiva.

Sobel and co-workers[11] in 1955 described an epidemic in a boys' camp characterized by mild pharyngitis with follicular tonsillitis. They expressed concern regarding poliomyelitis as many of the campers complained of headache, myalgias, and pains in the neck and back. The clinical features of this epidemic were well defined and were described in the following order: sore throat, headache, myalgia, eye discomfort, and abdominal symptoms with stiffness of the neck and back. Bacteriologic studies were unrevealing, but the virologic findings clearly proved that adenovirus type 3 was the cause of the epidemic. Huebner[7] states that types 3, 7a, and 14 have been most commonly associated, with pharyngoconjunctival fever, but types 1, 2, 5, and 6 have also been identified with this clinical syndrome. This entire group of diseases might be referred to as adenovirus infection.

Acute respiratory disease (ARD), due to type 4 adenovirus originally, is now also associated with types 7, 3, and 14. An acute febrile illness with pharyngitis characterizes this disease with cough, hoarseness, and chest pain representing

the most striking symptoms. The clinical spectrum extends from inapparent illness and mild colds to virus pneumonia as clearly pointed out by Hilleman.[5] The white blood count was over 10,000 per milliliter in the sickest individuals and temperature elevations ranged from 100° to 105° F., persisting from 2 to 12 days (with an average of 5) in the classic studies reported from Fort Leonard Wood by Hilleman and associates.[12] Berge[13] reported ARD among the recruits at Fort Ord, California, and described the illnesses as primary pharyngitis, febrile common colds, tonsillitis, and upper respiratory infection. In Berge's study type 4 adenovirus was isolated from many of the patients with tonsillitis. This type and type 7 were found in all of the clinical pictures which were presented, including primary atypical pneumonia and bronchitis.

The classic form of epidemic keratoconjunctivitis was found to be due to adenovirus type 8 by Jawetz and associates[14] in 1956. It was commonly found in workers in defense plants, particularly those subject to eye trauma. As a rule, there are few systemic symptoms caused by the type 8 virus. Permanent corneal opacities may rarely result from this type of infection.

Chany and co-workers[15] reported an epidemic of pneumonia, occurring in a hospital in Paris, which was fatal to several children. This epidemic was established as being due to adenovirus type 7a. There were approximately 20 patients with pneumonia; in 4 the illnesses were described as very severe, being fatal to 3 infants under 4 years of age. Gerbeaux[16] also reported a family epidemic caused by the same organism in which 3 children aged 4½ years, 21 months, and 3½ months were involved. The youngest had a mild illness with recovery, the 21-month-old infant had a serous effusion and recovered, and the 4½-year-old child died from virus pneumonia and encephalitis. Autopsy findings revealed bronchial necrosis and intranuclear inclusion bodies similar to those reported by Goodpasture in 1939.[17] Adenovirus, type 7a, was isolated prior to death from spinal fluid and from brain and lung tissues at the time of necropsy.

Successful vaccines prepared from some of the adenoviruses have been under study since 1955. Huebner and associates[18] showed that type 3 infection could be prevented in human volunteers and in 1956 Bell and associates[19] employed a trivalent vaccine made with types 3, 4, and 7. Loosli and co-workers[10] studied a formalinized vaccine made from types 3, 4, and 7 in naval recruits in San Diego. They concluded that the vaccine significantly reduced adenovirus infection at the Naval Training Center under study. Hilleman[20] in 1957 also studied all three types in a formalin-killed vaccine and showed a marked reduction in the incidence of adenovirus-caused disease in the immediate weeks following vaccination. In 311 vaccinated recruits they found only one patient with a proved infection in contrast to 61 patients among a similar number of controls.

ENTEROVIRUS DISEASES

The enteroviruses are characterized by the fact that they multiply in the human intestinal tract, and the most striking syndrome caused by them is aseptic meningitis. Nevertheless, diarrhea and acute respiratory disease are clearly identified with certain of these viruses. The enteroviruses include three types

of polioviruses, 25 types of Coxsackie A and 5 or 6 types of Coxsackie B, and the large group of ECHO (enteric cytopathogenic human orphan) viruses now containing more than 25 distinct types. Certain of the Coxsackie Group A agents cause acute pharyngitis or herpangina. Grippelike illnesses have been associated with type B agents, which most characteristically cause pleurodynia or Bornholm disease, as well as meningitis and myocarditis.

Ten years ago Dalldorf and associates[21] first identified a new virus which they isolated from patients who were being studied for poliomyelitis. Two groups, A and B, are recognized; the group A Coxsackie viruses cause flaccid paralysis and degeneration of muscles in suckling mice, and the group B agents cause encephalomyelitis with focal myositis in these same animals. Type A infections are frequently associated with vesicular pharyngitis or herpangina, whereas the B agents are commonly related to the syndrome of pleurodynia and aseptic meningitis. Vesicular pharyngitis was first described by Zahorsky[22] in 1920 as an acute febrile disease in children involving the pharynx and soft palate.

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Coxsackie viruses are now known to cause disease in man throughout the world. Coxsackie agents produce disease primarily during the summer and fall months and appear commonly to infect children, causing family epidemics. The incubation period averages 4 to 5 days in most instances.

The clinical features of vesicular pharyngitis or herpangina are dysphagia, general aching, pharyngeal erythema, chest pain, chills, and acute pharyngitis. The onset of disease is usually sudden. Fevers are of low grade, averaging 100° to 102° F., rarely reaching 105° F. The duration of fever in the uncomplicated illness is 2 to 4 days in the majority of the patients. Characteristic lesions are gray-white papular vesicles measuring 1 to 2 cm. in diameter. They are found on the anterior pillars, soft palate, uvula, and tonsils. Ulceration takes place and may persist for a week to 10 days. The lesions should be differentiated from infectious gingivostomatitis caused by herpes simplex virus. Vesicular pharyngitis due to many of the Coxsackie A agents commonly occurs in the summer months, whereas herpes simplex stomatitis may be seen in any season of the year. Rasmussen[23] reported an epidemic in which acute pharyngitis was the main sign of Coxsackie A virus infection and no vesicular lesions were observed.

Epidemic pleurodynia is the main clinical picture caused by the Coxsackie B viruses and excruciating chest pain may be the primary symptom. Certain types in both groups A and B have been shown to cause acute respiratory tract infection. The symptoms are usually self-limited and cases of virus pneumonia caused by either of the Coxsackie groups of viruses are very rare.

ECHO (enteric cytopathogenic human orphan) viruses were isolated from stool specimens prior to their identification with disease. Certain of the 25 types including 8, 10, 11, and 20 appear to cause acute respiratory tract infections, particularly in the colder months of the year.

Cramblett and associates[24] studied 6 infants with respiratory tract infection caused by type 20. The major manifestations were fever, coryza, erythema of the pharynx and eardrums, and abnormal stools. Coryza with sneezing and irritability occurred in all patients. Cough was also a striking symptom in 5 of the 6 original patients. Redness of the pharynx in the tonsillar area was observed,

as well as meningitis with suppurative otitis media in one patient. All of the patients had abnormal stools with frank diarrhea in 4. The white blood cell counts were not characteristic but 4 of the 6 patients had positive roentgenograms of the chest with increased markings, hilar lymphadenopathy, and pulmonary infiltrations. Virus studies showed that the causative agent was similar to the agents in the ECHO group, and is now clearly identified as ECHO, type 20.

The ECHO viruses share the following characteristics: they produce cytopathogenesis in monkey and human cells in tissue culture, but are not neutralized by poliovirus antisera. They do not cause disease in infant mice, and are not neutralized by Coxsackie antisera. They are neutralized by specific convalescent sera and by human gamma globulin.

The spectrum of illness produced by the ECHO viruses is quite varied Ramos-Alvarez and Sabin[25] showed that certain of these viruses were capable of causing diarrhea in infancy. Some of the ECHO group have been related to epidemics of common respiratory disease, sometimes associated with diarrhea and steatorrheic enteritis in children and adults. There is a high incidence of aseptic meningitis caused by these viruses but rarely followed or accompanied by paralysis. In patients with acute febrile illnesses, a high incidence of rash has been described, particularly with types 9 and 16. Diagnosis is readily accomplished by isolation of virus from stool and spinal fluid.

The ECHO viruses are now well established as etiological agents of disease in man, but many types have still to be studied in greater detail. The enteroviruses are associated with the following diseases: (1) polioviruses—paralysis (complete to slight muscle weakness), aseptic meningitis, and undifferentiated febrile illness particularly during the summer; (2) Coxsackie viruses, group A—herpangina (types 2, 4, 5, 6, 8, and 10), aseptic meningitis (types A-7 and A-9), undifferentiated febrile illness particularly during the summer, and febrile illness with rash (type A-9); (3) Coxsackie viruses group B—pleurodynia (Bornholm disease), myocarditis or encephalomycarditis during neonatal period and early childhood, mild paralysis (?) or encephalitis, aseptic meningitis, and undifferentiated febrile illness with pharyngitis; (4) ECHO viruses—Boston exanthem (type 16), summer diarrhea of infants and children (type 18 and others), mild paralysis (?) (types 6 and 9) or encephalitis (type 9), aseptic meningitis (types 2, 3, 4, 5, 9, 14, 16, and 21), and undifferentiated febrile illness particularly during the summer.

During the Second World War primary atypical pneumonia became a popular diagnosis and a rather characteristic syndrome was described. The clinical features were cough, sputum, and pulmonary infiltrations which were usually demonstrated radiologically. Routine laboratory tests were normal and no pathogenic bacteria were cultured from these patients. The syndrome was closely related to that caused by many known agents, including bacteria and fungi, psittacosis and influenza viruses. Two laboratory procedures, the cold hemagglutination and streptococcus MG agglutination tests, were often found to be positive, particularly in the severely ill patients with this syndrome. Although this disease is commonly considered to be viral in origin, final proof is lacking. The fact that many known viral infections may produce pneumonia in a certain percentage of patients serves to add further confusion to the identity of primary

atypical pneumonia. In 1944, Eaton, Meikeljohn, and van Herrick[26] reported the isolation of an agent from patients with primary atypical pneumonia. Recently, Liu and Coffin[27] reported identifying certain viral agents by indirect fluorescein antibody tests. They showed an antigenic relationship to the agent originally isolated by Eaton and co-workers.[26]

Virus pneumonitis is recognized as part of the spectrum of many of the respiratory viral infections, particularly the influenzas and the adenoviruses. When the cause is identified, the case may then be removed from the group of patients with primary atypical pneumonia of unknown etiology. Dingle and Feller[28] point out that more than one unidentified agent may produce the syndrome of primary atypical pneumonia of unknown etiology and that the same agent or agents may induce both a pneumonic and a nonpneumonic form of disease.

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TREATMENT

There is no specific drug or therapy available for most of the commonly recognized primarily viral infections. Specific treatment has been found to be helpful in certain viral infections, such as those caused by the psittacosis group of agents and in certain of the rickettsial infections. Primary pharyngitis of viral origin does not require specific therapy as these are self-limited illnesses from which recovery is uneventful. When the primary disease advances to involve the pulmonary tissues, it becomes more difficult to withhold antibiotic therapy. It is often recommended not to treat the primary disease, but to prevent the common secondary complicating organisms from causing disease. It is well known that many primary viral infections may become complicated by secondary bacterial infection.

In the case of primary atypical pneumonia there are many conflicting reports in the literature concerning the value of specific therapy. Certain of the broad spectrum antibiotics have been advocated, but there is quite general agreement that the sulfonamide drugs and penicillin have no beneficial effect. Improvement is often observed following the use of broad spectrum antibiotics. Dingle and Feller[28] suggest that certain of the broad spectrum antibiotics are antipyretic in their effects, which may account for the apparent improvement in many patients. Mixed infections of all sorts are always potentially in the picture, and when the patient is ill enough to be treated for acute pneumonitis, presumably of viral origin, the small risk of antibiotic therapy is probably outweighed by the seriousness of the patient's illness, and thus antibiotic therapy may be justified.

Therapy designed to promote rest and control spread of infection to others is a prime consideration. Increasing the humidity of the room is often beneficial to patients who are suffering from cough and laryngeal symptoms, such as croup. The spread of infection may be greatly reduced by increasing the humidity in the atmosphere as shown by Loosli and associates[29] in the case of experimental influenza.

Treatment of acute infections in the upper respiratory passages by means of posture, placing the baby in a prone position and elevating the foot of the bed, is sometimes advised. Inasmuch as the primary mechanism of the inception

of pneumonia is related to aspiration, its prevention by posture may be helpful. Coughs are often benefited by placing the baby in the prone position. Foods and fluids should be offered as desired, but not forced. The avoidance of drafts and undue exposure are common and approved methods of treatment.

OTHER RESPIRATORY VIRUS DISEASES

Several other as yet not well-established viral infections of the respiratory passages will be mentioned briefly. A new virus originally discovered by Morris, Blount, and Savage[30] caused spontaneous respiratory tract infection in chimpanzees. The virus when grown in tissue culture was capable of infecting other chimpanzees and produced a coryzalike illness. Chanock, Roizman, and Myers[31] isolated an agent from infants with croup and pneumonia which proved to be very similar to the viruses isolated from the chimpanzees. Serologic tests revealed that this infection occurred in 9 of 13 children with pneumonia studied by them.

In 1956, 20 or more strains of virus were isolated by Price[32] at Johns Hopkins from adults and children suffering from sore throats and mild respiratory symptoms. Price designated this agent as J. H. virus. Following passage in monkey kidney tissues, cytopathology occurred which could be neutralized by the convalescent serum from recovered cases. A vaccine prepared from monkey kidney cultures has been employed successfully in volunteer studies.

Serologic evidence for the existence of an antigenically related agent in England was presented by Tyrrell and Bynoe,[33] although their attempts at direct isolation of virus from adults and children with colds failed.

In 1957, Pelon and Mogabgab[34] reported an agent causing mild respiratory disease isolated from pharyngeal washings from naval recruits at Great Lakes Naval Training Station. This material produced typical cytopathology in monkey kidney tissue cultures which could be neutralized by convalescent serum from recovered patients. The illnesses were described as coryzal with sore throat, cough, and low grade fevers.

An apparently new virus (the Coe virus) was recovered from patients with mild pharyngitis by Lennette and associates[35] in 1958. They were able to differentiate this agent from practically all of the other viruses referred to in this chapter, and thus gave it a new name after one of the 4 strains which they isolated. The clinical spectrum and epidemiology of the Coe virus will have to await further study in larger groups of cases. It has recently been shown to be related to the parainfluenzas.

Undoubtedly there remain many unknown viral diseases of childhood. In the past few years, however, many pieces have been added to the etiological pie, and when these are well studied epidemiologically it is possible that the percentage of unknown and unclassified illnesses will be greatly reduced. Although the over-all picture may appear discouraging, certainly in community and family epidemics, a high percentage of disease may be explained etiologically when approached and studied from this point of view. Isolation of, and serologic studies for, common viruses are now available in many city, county, and state laboratories. Results are, as a rule, not practically available to the practicing

clinician and he still must rely on his epidemiologic knowledge and clinical skill in evaluating his patients' history and physical findings. When we train ourselves to think etiologically and not take these common diseases for granted, a great deal may be accomplished in increased understanding and benefit to our patients.

REFERENCES

1. Vogel, J., and Shelokov, A.: Adsorption—Hemagglutination Test for Influenza Virus in Monkey Kidney Tissue Culture, Science **126**:358, 1957.
2. Chanock, R. M., Parrott, R. H., Cook, K., Andrews, B. E., Bell, J. A., Reichelderfer, T., Kapikian, A. Z., Mastrota, F. M., and Huebner, R. J.: Newly Recognized Myxoviruses From Children With Respiratory Disease, New England J. Med. **104**:555, 1958.
3. Reichelderfer, T. E., Chanock, R. M., Craighead, J. E., Huebner, R. J., Turner, H. C., James, W., and Ward, T. G.: Infection of Human Volunteers With Type 2 Hemadsorption Virus, Science **128**:779, 1958.
4. Chanock, R. M.: Association of a New Type of Cytopathogenic Myxovirus With Infantile Croup, J. Exper. Med. **104**:555, 1956.
5. Hilleman, M. R.: Epidemiology of Adenovirus Respiratory Infections in Military Recruit Populations, Ann. New York Acad. Sc. **67**:262, 1957.
6. Hilleman, M. R., and Werner, J. H.: Recovery of New Agent From Patients With Acute Respiratory Illness, Proc. Soc. Exper. Biol. & Med. **85**:183, 1954.
7. Huebner, R. J.: Illnesses Due to Adenoviruses, Modern Medicine **26**:103, 1958.
8. Jordan, W. S., Jr.: The Frequency of Infection With Adenoviruses in a Family Study Population, Ann. New York Acad. Sc. **67**:273, 1957.
9. Evans, A. S.: Acute Respiratory Disease in University of Wisconsin Students, New England J. Med. **256**:377, 1957.
10. Loosli, C. G., Tipton, V. C., Warner, O., Smith, M., Johnston, P. B., and Hamre, D.: Adenovirus Vaccine Evaluation Study in Naval Recruits, Proc. Soc. Exper. Biol. & Med. **98**:583, 1958.
11. Sobel, G., Aronson, B., Aronson, S., and Walker, D.: Pharyngoconjunctival Fever, A.M.A. J. Dis Child. **92**:596, 1956.
12. Hilleman, M. R., Werner, J. H., Adair, C. V., and Dreisbach, A. R.: Outbreak of Acute Respiratory Illness Caused by RI-67 and Influenza A Viruses, Fort Leonard Wood, 1952-1953, Am. J. Hyg. **61**:163, 1955.
13. Berge, T. O., England, B., Mauris, C., Shuey, H. E., and Lennette, E. H.: Etiology of Acute Respiratory Disease Among Service Personnel at Fort Ord., Calif., Am. J. Hyg. **62**:283, 1955.
14. Jawetz, E., Hanna, L., Kimura, S. J., and Thygeson, P.: A New Type of APC Virus From Follicular Conjunctivitis, Am. J. Ophth. **41**:231, 1956.
15. Chany, C., Lepine, P., Lelong, M., Le Tau Vinh, Satge, P., and Virat, J.: Severe and Fatal Pneumonia in Infants and Young Children Associated With Adenovirus Infection, Am. J. Hyg. **67**:367, 1958.
16. Gerbeaux, J., Heber-Jouas, J., Masse, N., and Beauchef, A.: Épidémie familiale de maladie à virus du groupe APC chez trois Enfants (un cas mortel), étude clinique, anatomique et virologique, Bull. Soc. méd. Hôp. Paris **73**:519, 1957.
17. Goodpasture, E. W., Auerbach, S. H., Swanson, H. S., and Cotter, E. F.: Virus Pneumonia of Infants Secondary to Epidemic Infections, Am. J. Dis. Child. **57**:997, 1939.
18. Huebner, R. J., Bell, J. A., Rowe, W. P., Ward, T. G., Suskind, R. G., Hartley, J. W., and Paffenberger, R. S., Jr.: Studies of Adenoidal-Pharyngeal-Conjunctival Vaccines in Volunteers, J.A.M.A. **159**:986, 1955.
19. Bell, J. A., Hantover, M. J. Heubner, R. J., and Loosli, C. G.: Efficacy of Trivalent Adenovirus (ACP) Vaccine in Naval Recruits, J.A.M.A. **161**:1521, 1956.
20. Hilleman, M. R.: Epidemiology of Adenovirus Respiratory Infections in Military Recruit Populations, Ann. New York Acad. Sc. **67**:262, 1957.
21. Dalldorf, G., Sickles, G. M., Plager, H., and Gifford, R.: Virus Recovered From Feces of "Poliomyelitis" in Patients Pathogenic for Suckling Mice, J. Exper. Med. **89**:567, 1949.
22. Zahorsky, J.: Herpetic Sore Throat, South. M. J. **13**:871, 1920.
23. Rasmussen, A. F., Cline, F. A., and Borge, A. F.: Coxsackie Virus Infections in Northern Wisconsin, Wisconsin M. J. **52**:129, 1953.
24. Cramblett, H. G., Rosen, L., Parrott, R. H., Bell, J. A., Huebner, R. J., and McCullough, N. B.: Respiratory Illness in Six Infants Infected With a Newly Recognized ECHO Virus, Pediatrics **21**:168, 1958.
25. Ramos-Alvarez, M., and Sabin, A. B.: Characteristics of Poliomyelitis and Other Viruses Recovered in Tissue Cultures From Healthy American Children, Proc. Soc. Exper. Biol. & Med. **87**:655, 1954.

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26. Eaton, M. D., Meiklejohn, G., and van Herrick, W.: Studies on Etiology of Primary Atypical Pneumonia: Filterable Agent Transmissible to Cotton Rats, Hamsters, and Chick Embryos, J. Exper. Med. **70**:649, 1944.
27. Liu, C., and Coffin, D. L.: Studies on Canine Distemper Infection by Means of Fluorescein-Labeled Antibody. I. The Pathogenesis, Pathology, and Diagnosis of the Disease in Experimentally Infected Ferrets, Virology **3**:115, 1957.
28. Dingle, J. H., and Feller, A. E.: Noninfluenzal Viral Infections of the Respiratory Tract, New England J. Med. **254**:465, 1956.
29. Loosli, C. G., Lemon, H. M., Robertson, O. H., and Appel, E.: Experimental Air-Borne Influenza Infection; Influence of Humidity on Survival of Virus in Air, Proc. Soc. Exper. Biol. & Med. **53**:205, 1943.
30. Morris, J. A., Blount, R. E., Jr., and Savage, R. E.: Recovery of a Cytopathogenic Agent From Chimpanzees With Coryza, Proc. Soc. Exper. Biol. & Med. **92**:544, 1956.
31. Chanock, R. M., Roizman, B., and Myers, R.: Recovery From Infants With Respiratory Illness of a Virus Related to Chimpanzee Coryza Agent (CCA). I. Isolation, Properties and Characterization, Am. J. Hyg. **66**:281, 1957.
32. Price, W. H.: Isolation of New Virus Associated With Respiratory Clinical Disease in Humans, Proc. Nat. Acad. Sc. **42**:892, 1956.
33. Tyrrell, D. A. J., and Bynoe, M. L.: Inoculation of Volunteers With J. H. Strain of New Respiratory Virus, Lancet **2**:931, 1958.
34. Pelon, W., and Mogabgab, W. J.: Problems in Characterizing and Identifying and Apparently New Virus Found in Association With Mild Respiratory Disease in Recruits, Ann. New York Acad. Sc., **67**:403, 1957.
35. Lennette, E. H., Fox, V. L., Schmidt, N. J., and Culver, J. O.: The Coe Virus, an Apparently New Virus Recovered From Patients With Mild Respiratory Disease, Am. J. Hyg. **68**:272, 1956.

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CHRONIC ALLERGY—CRIPPLER AND KILLER OF CHILDREN

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ALLERGY is a forgotten cause of crippling disease in children and is almost never considered as a major cause of death at this age. Yet allergy is both of these things for many children, for at least one child in ten, and probably more accurately one child in five, has major allergy, and death from asthma is three times as frequent as from diphtheria in early childhood.[1]

A recent survey of the incidence of major allergy in a child population by Rappaport, Appel, and Szanton,[2] showed that 19.5 per cent of children under 14 in the group they studied had infantile eczema, hay fever, and/or asthma. If this percentage is applied to the United States as a whole, it is estimated that 3,500,000 children are affected with this serious handicapping medical condition. The tragic fact that 2 of every 3 victims never get medical treatment is the most shocking and disgraceful finding which their survey unearthed. With major allergy afflicting a total of 24.5 million Americans it is not surprising that antiallergic drugs were in eighth place of all prescriptions filled by U. S. pharmacists in a 4-month comparison in April-July, 1959, and comprised 50 per cent of prescriptions refilled.[3] If one includes a portion of the dermatological prescriptions which were in fourth place, nose, cold, and cough preparations, eighteenth and nineteenth; metabolic drugs, seventh; and anti-infective drugs, second; of which some, certainly, were destined for use in problems of allergy, this represents a major portion of the medication prescribed for Americans in the spring and summer of the year in question.

In spite of the massive medication for allergy, there are many children whose symptoms are not completely controlled, and who go about half sick or who are frankly ill. Why do we do so little? Is it because their complaints often begin with common symptoms such as a runny nose or a little cough? Is it because we expect a skin eruption to clear up by the age of 2, that we allow a disfiguring rash to go untreated? Is it because we all know so many people with allergy or because so many of us choose to ignore our own allergies that we blind ourselves to this staggering group? We expect children to outgrow their allergies, forgetting that most of the adults with allergy had the onset of their trouble before 10 years of

age. Until we recognize that allergy is a lifelong condition, and one which is of major economic importance in impaired efficiency for the mild case, and a serious economic drain on families in more severe forms, we are neglecting one of America's major health problems. It is not uncommon to have parents of modest means with an allergic child relate that they have spent $500 to $1,000 or more on purely symptomatic treatment exclusive of hospitalization in a single year, prior to seeking any help in specific treatment. Medicare figures for 1958, comparing hospital costs for various illnesses, as cost per case, report for asthma the amount of $187, with 5.9 days of hospitalization.[4]

Even this impressive sum of money does not accurately reflect the cost of hospitalization for asthma since Medicare allowances are only for acute life-threatening emergencies of chronic ailments, and thus many instances of serious asthma are not eligible for Medicare. Far more children are seriously ill with asthma and cared for at home, or hospitalized at parents' expense, than are covered by any type of insurance program. Most, if not all, insurance companies are reluctant to issue either hospital or life insurance policies to an asthmatic individual whose symptoms began in childhood, regardless of how well controlled the allergy may be.

The cost of hospitalization for an infant with severe eczema is impossible to determine accurately, but on the basis of personal experience this frequently represents one to 3 weeks or more of hospitalization. Our most glaring example of this is a medically indigent lad who had 22 hospital admissions for eczema and asthma by the age of 5 years, plus 6 months in a nursing home, and one year in an orthopedic hospital for treatment of osteomyelitis which developed as a complication of his infected eczema. The 8 Duke admissions, covering 189 days, cost $4,373.97. We cannot determine the cost of the previous 14 admissions in other hospitals or the cost of his 6 months in the nursing home and the orthopedic hospital.

None of the available statistics give an accurate picture of the number of allergic children at home, who are not sick enough to be hospitalized, but who are not well enough to lead a normal life. The number of these children can only be surmised from the new surveys available, and on the basis of the impression of many pediatricians who state that exclusive of well-baby care, and the contagious diseases of childhood, allergic problems comprise the largest single group of disorders in their practice. If Rappaport's[2] figures are representative of the country as a whole, and we have reason to feel they are conservative, then for every child with allergy who receives medical attention there are 2 more whose allergy problems go unattended. An amplification of an extensive house-to-house survey of the incidence of allergy in a large group of American children is urgently needed to bring the magnitude of the problem into proper focus for laymen, health and welfare officials, and physicians. When the details of the current sickness survey of the U. S. P. H. and Bureau of Census are available there may be clarification of the role which asthma plays in the number of school days lost for chronic respiratory disease, the largest single chronic disease figure reported.[5] Allergic diseases should be made reportable conditions for state and U. S. vital statistics.

How does allergy rank as a killer of children? In 1956 there were 145 deaths from asthma in children under 5 years of age,[6] in 1957 there were 139. In 1957 there were 53 deaths from acute poliomyelitis in children under 5 years.[1] In our own practice there have been 5 deaths from asthma in steroid-treated asthmatic children in the past 5 years in contrast to 2 deaths due to pneumonia in asthmatics in the preceding 15 years. If we compare the number of deaths from asthma in children as reported in the U. S. Vital Statistics with deaths from other so-called "preventable" diseases, and from some of the diseases which cause us just concern as health hazards, we find that asthma deaths are surprisingly high (Table I).

Fortunately, allergic rhinitis is not associated with any mortality, but it accounts for many important medical problems in the young child. The child with this condition is prone to develop a characteristic pinched allergic or adenoidal facies from chronic mouth breathing. This would be worrisome if for no other than cosmetic reasons, but more serious is the narrow dental arch which results in malocclusion and the need for prolonged and extensive orthodontic treatment. Children with allergic rhinitis are subject to prolonged respiratory infections as they go through childhood and, as they grow older, chronic sinusitis and nasal polyposis may plague them. Their hearing is often impaired, as a result of either complicating acute and chronic otitis media which accompanies their repeated respiratory infections, or equally often a persistent secretory otitis media, which results in varying degrees of deafness.

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TABLE I. U. S. DEATHS FROM "PREVENTABLE" DISEASES, 1957*

	UNDER 5 YR. OF AGE	ALL AGES
Dysentery†	271	440
Tuberculosis†	221	13,324
Pertussis	173	183
Asthma	139	6,677
Diabetes	54	27,180
Acute poliomyelitis	53	221
Late effects of acute poliomyelitis	2	148
Diphtheria	43	81
Rheumatic fever, acute	34	900
Typhoid	4	34

*Vital Statistics of the United States, U. S. Dept. of Health, Education, and Welfare, 1957, Vol. 2, Table 51.

†All types.

The effect of chronic nasal obstruction on mental performance and behavior has never been thoroughly explored, to my knowledge, but one gains the impression from parents and teachers that there is a definite improvement in both of these functions in children when nasal allergy is controlled and a deterioration

when it is symptomatic. Appetite and weight often increase in children whose allergy is treated successfully. It is interesting to speculate that this may be due to an improvement in or sharpening of the sense of small.

Along with allergic rhinitis a significant degree of allergic conjuctivitis may be present, and with this frequently there are behavior disorders and school problems of major importance. Children with these afflictions are so miserable with itching eyes, photophobia, and lacrimation that they do little but "dig at" their eyes, cannot play or study normally, and become exceedingly difficult to manage in the home. We have seen a few youngsters who developed corneal ulcers with scarring of the cornea from pressure of redundant allergic granulation of the upper lid on the cornea, although fortunately this is a rare complication. When this does occur, there is a threat to vision, and only then can one enlist help from the Blind Commissions for an indigent child.

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The most common complication of allergic rhinitis is bronchial asthma, and a high percentage of children who have allergic nasal symptoms at 2 to 5 years of age have asthma before they are ten. Some asthmatic individuals, however, appear to have no antecedent allergic disease. The nasal and bronchial allergy may develop simultaneously, or less often the asthma may be accompanied by relatively few, or insignificant symptoms in the upper respiratory tract.

Infantile eczema has been followed by asthma in 33 per cent of a series of patients which we analyzed.[7] Since most of the children were followd only for 5 years, it is quite likely that the percentages of 53 and 66 which have been reported by Glaser[8] and Kraepelien[9] give a truer picture of the incidence of the development of asthma in eczematous infants.

An appreciable number of infants who have infantile eczema will pass on through childhood with chronic eczema, which merges without clearing into neurodermatitis of older childhood and adult life. The inconvenience, the embarassment of chronic skin eruption, and the ever-present hazard of secondary infection in these persons may be a very serious problem. A rather extensive collection of psychiatric studies on children and adults with chronic eczema has shown that as the condition becomes more and more chronic the psychic overlay becomes greater and the skin becomes a sounding board for every stress the person experiences in life.[10-13]

The child with severe or recurrent urticaria or angioedema and the child who develops a serious allergy to insect bites demands attention because of the immediate threat to life if vital air passages are involved. Once the dramatic danger is over, and one settles down to the laborious task of trying to establish the cause of the eruption, these children also come to present difficult and expensive diagnostic and therapeutic problems. The incidence of these forms of allergies is low compared to that of the three major types of allergy, and therefore, while they pose a problem to the physician and make life miserable for the patient, their relative number is low compared to that of other allergic disorders.

The major crippling and life-threatening allergic condition in children is asthma. The word evokes the familiar picture of a child fighting for breath, often cyanotic, with exhausting, hacking, nonproductive cough, and audible wheezing. The older child sitting on the edge of the bed supporting himself on extended arms,

shoulders hunched, with suprasternal retraction, chest heaving, and his position relatively fixed, with shallow inefficient excursions, using all accessory muscles of respiration, is a characteristic and unforgettable sight. The infant assumes a position on all fours, or restlessly tosses about the bed, or in the mother's arms, with shallow panting respiration, often pale, sweaty, and cyanotic. The effort required for breathing, plus interference with sleep, rapidly exhausts the child with an acute asthmatic attack. The patient's distress is so great that efforts for relief are apt to be promptly carried out. The relief obtained from a variety of medications is often so rapid, and complete in the uncomplicated acute attack, that a certain complacency may develop in attendants and parents that all attacks will respond in such satisfactory fashion. It is only when one severe episode does not subside, or the attacks come in close succession or never quite clear completely, that the picture of chronic asthma develops.

The state of chronic asthma is difficult to define since the child with chronic asthma may be one who wheezes mildly and shows signs of obstructive emphysema of a moderate degree most, if not all, of the time. The individual who has dyspneic attacks which occur with such frequency that he has relatively few free periods may also be considered as an individual with chronic asthma. A child whose attacks of difficulty in breathing are separated by months of freedom cannot strictly be said to have chronic asthma although he may have periods each year when he is greatly incapacitated by his disease. In terms of definition by the child or his parents, who state that wheezing is present most of the time, or that wheezing interfers with normal childhood activities, including play and school this would certainly fall into the category of chronic asthma.

It is surprising, when one considers the over-all frequency of the allergic diseases and the major significance of asthma among this group of illnesses, that so little attention has been paid to the rehabilitation of the child with chronic asthma. This probably stems from concentration on relieving urgent symptoms and from our ignorance or unawareness of the true incidence of asthma among the child population.

How can the child with chronic asthma be rehabilitated? The usual approach to the problem is either that of exclusively symptomatic treatment or of exclusively allergic management. It immediately appears that children with chronic asthma can be cared for in special facilities. These are limited in comparison to the numbers of children who need and could be benefited by care of this sort. It then devolves upon the child's physician and parents to attempt some rehabilitation program themselves. How can this best be approached? First, by a careful evaluation of the child as a whole, assessing the severity of the asthma as a disease problem just as one would approach the problem in a diabetic person by determining the severity of the diabetes, or in one with paralytic poliomyelitis by muscle evaluation, or in tuberculosis by determining the extent and activity of the process, or in a cardiac problem by assessing not only the nature of the lesion but the individual's cardiac function. In the same way one can approach the study of the chronically asthmatic child. First, one estimates the severity of the asthmatic attacks. How sick does the child become with asthma? How rapidly does the asthma develop? Does he become cyanotic? How often do these

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episodes occur and how long do they last? What sort of treatment is required to bring relief of symptoms? There is a vast difference between the severity of asthma which requires every possible therapeutic means to relieve the dyspnea and the asthma which may be subjectively as distressing but which is relieved by the proper administration of a small dose of oral medication. This information is, of course, known to the physician who attends the child or can be ascertained in very short order.

The second point is to learn the extent of the physical handicap which the child suffers. This requires a complete physical examination with special attention to nutrition and pulmonary function. If special tests are not feasible, and these are often impractible in young children, one can obtain some idea of the child's

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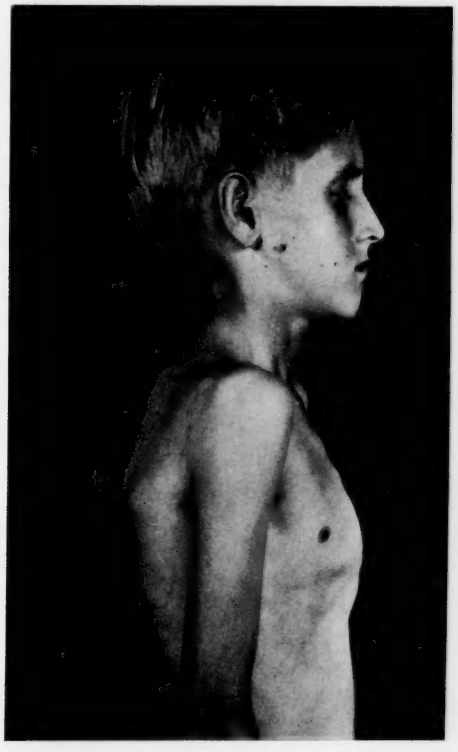

Fig. 1.—A 14-year-old boy with chronic asthma, allergic rhinitis since 3 to 4 months of age. Note marked emphysema and typical allergic facial deformity.

exercise tolerance. Does minor activity produce wheezing and dyspnea? Does the child keep up in physical sports with other children his size? Does he voluntarily lead a sedentary life? Can he ride a bicycle? Does he become excessively fatigued after exercise? Is chest deformity present? A careful examination of the chest with attention to the lung expansion and to the descent of the lung bases and measurement of the anterior-posterior diameter of the chest will give an

idea of the degree of emphysema which may be present (Fig. 1). This is suggested by faint and distant breath sounds and can be confirmed by x-ray if necessary. A hemoglobin or hematocrit which is definitely higher than the expected normal range for the child's age should also make one suspicious that a degree of compensatory polycythemia due to inefficient oxygenation is present. What, if any, complications are present in connection with the asthma? The presence of other allergic symptoms such as allergic rhinitis and eczema should be noted. Has atelectasis occurred? Atelectasis of the right middle lobe area is seen so frequently in asthmatic children who have persistent symptoms that it should be kept in mind in anyone with chronic asthma until it has been carefully excluded. It is obvious, of course, that one must be alert for other conditions, which may be characterized by wheezing of one type or another. The whole gamut of differential diagnosis of chronic lung disease, presence of foreign bodies, and vascular anomalies must be ruled out. It must be borne in mind, of course, that any child may have the misfortune to have more than one pathologic process.

The next step consists of identifying the specific allergic factors in the particular case. This, of course, is the aspect of allergy which is uppermost in the parent's mind and frequently in the physician's mind when the child is finally brought to an allergist. Knowing that asthma is one of the diseases which may be due to a specific antigen-antibody reaction, there is a tendency in our thinking to assume that once these antigens have been identified the problem is solved. In some instances, this may be true and, in all children, all allergic factors should be sought out. One should constantly bear in mind that new allergies may appear and that many unsuspected ones may still be present in the child who has persistent symptoms.

However, in many children the so-called nonspecific factors are of equal importance not only in precipitating attacks but in perpetuating them. One of the principal factors is infection. Each child who has chronic asthma should be carefully screened for a focus of infection which will serve to continue bronchial inflammation. Whether this focus is in the child or comes from a family source as recurrent reinfection, or is due to the child's individual susceptibility to infection are all questions which have to be considered for each individual. In some children this will be a minor problem. In some children it will not be present. In others it may serve as the key to the solution of intractable asthma. In some children persistent infection may result in chronic bronchitis or bronchiectasis.

The next nonspecific factor to consider is the diet. In many children who have recurring episodes of asthma, the diet is limited because of either known or suspected food allergens. In others, the diet has become an abnormal one as a result of the child's whims and capricious appetite. In taking a detailed dietary history, one is impressed with the fact that many children subsist on such a refined carbohydrate diet that they would be well on the way to vitamin deficiency were not some of our foods fortified with additional vitamins. Or, the child who has chronic asthma will drink excessive quantities of milk or subsist primarily on sweetened carbonated beverages, starchy foods, and desserts. In younger children one gains the impression that there is often a disinterest in meats and green vegetables. Apparently with some children these are acquired

tastes and when they feel bad they are averse to and disinterested in a well-balanced variety of foods. Mothers may develop fears and phobias regarding foods and this further complicates the problem. In other instances, the general discipline and routine of the child are so disrupted by recurring episodes of illness that a free choice of diet is allowed, and this may not always result in the well-balanced intake which was observed in Davis' classic experiments with children who were given access only to a variety of simple foods.

Airborne irritants such as smokes of different types, chemicals from industrial areas, fumes from paints and insecticides may all serve to produce bronchial spasm in a child who has asthma. This is an aspect of the causation of asthmatic attacks of which patients and parents appear to be relatively unaware. The common observation repeately reported by parents, that the child develops asthma when exposed to temperature changes such as while sitting in a draft, while getting chilled after taking a bath, when the hair is washed, or when going swimming, is another example of a physical change which may precipitate recurring episodes of asthma. It is surprising that few people ever take the logical step toward developing a tolerance to temperature changes in these children by deliberate small exposures to increasing ranges of temperature. This vasomotor instability is one of the common nonspecific mechanisms in producing allergic symptoms and one which is easily overlooked in treatment. Changes in humidity are also noted in some cases to be followed by asthmatic attacks. At times this can be controlled by air-conditioning or by climate change.

Fatigue is an extremely important factor in producing asthmatic attacks and is one which is not appreciated by parents as frequently as one would expect. The child who has lost many hours of sleep from wheezing will also have spent more than the normal amount of energy in the simple function of breathing and is a child who remains chronically tired. Such children are often allowed to drift into poor sleeping habits and they are candidates for the development of behavior problems in association with their sleep. A parent's apprehension regarding the child's possible illness during the night may be the initiating motive for sleeping with the child.

The overconcern of the parents may be the reflection of some deep-seated rejection of the child. Extensive psychiatric studies on allergic children by Miller and Baruch,[14,15] have shown many instances in which maternal rejection was an important factor in asthma. Other more complicated psychiatric problems have been found in allergic children in cases where the rejection apparently rose from the child and was a mutually interdependent problem. The families of allergic children frequently have other members with allergy and experience with the illness in the relatives may color the reaction toward the child. Sometimes the parents have a definite fear of death from asthma and this is present in the patient, perhaps expressed or unexpressed. One frequently hears in the course of the presentation of the child's history, "I thought he would die." If one glances at the child in these situations, he will often find that the child shows by his attitude that he too agrees with the parent and this is something which he also fears. The child from a broken home, the child whose parents work, is likely to have more emotional problems than the child whose background is that of a

stable, warm, firm family relationship. The interpersonal problems have a direct bearing, and in some cases assume a paramount position, in the precipitation of asthmatic attacks. It is extremely rewarding to ask some direct questions of the patients and to find out from the child himself exactly what his feelings are regarding his illness since frequently the parent takes over the entire process of reporting the symptoms. In children who are inarticulate or who are too young to express themselves, allowing them access to drawing materials or encouraging them to draw whatever they choose may give illuminating insight into their reaction toward their family contacts and toward their illness.[16]

The relationship of the child to animals is another area which is frequently worth exploring from the emotional standpoint. To an allergist who feels that he has demonstrated that contact with a pet is responsible for allergic symptoms it is a baffling situation to find that he is met with obstacles from all sides in separating the child from the pet not only from the patient but even more strongly from the parents. We often find after repeated suggestions, insistence, and even direct orders to break this contact, that the patient still returns with his ailment and with his pet. This may represent some deep-seated denial of the disease or it may represent some more deep-seated need for an expression of emotions which cannot be displayed toward family or other human contacts. The peculiar dependence upon animals which many allergic children show is an area which has not yet received sufficient investigation from the psychiatric viewpoint and which we are currently studying.

We now turn to the treatment of the chronically asthmatic child. From the analysis of the severity of the asthma, the extent of the physical handicap which is produced, and identification of both the allergic and nonallergic factors, one can proceed to the correction and the adjustment of those things which are pertinent in any particular case. In some children this will be extremely simple. In others it will be necessary to attempt to correct a variety of related and associated physical defects and emotional problems. The removal of the allergens may be a simple matter or it may be met with much resistance on the part of patient and parents. It may be advisable to desensitize the child. The identification of the nonspecific irritants and factors is frequently accomplished by having parents or child, if he is old enough, keep a detailed record of the circumstances which surround each episode of asthma. Or if the symptoms are continuous, a sample daily record of activities, places where attacks occur, weather conditions, diet, etc., may give the trained observer clues about specific allergens which were unsuspected from the direct questioning of the parents or the patient.

The next major point in the treatment of chronic asthma is the correction of the mechanical obstruction of the airway by excessive secretions and edema. In part this can be accomplished by the use of corrective breathing exercises and in some more severe instances by bronchoscopy. This can be aided by the judicious use of bronchodilators and expectorants and by restrained use of antihistamines which decrease mucosal edema. The breathing exercises which were originally described by the Asthma Research Council[17] have been modified by many physical therapists to include exercises for accessory muscles such as the abdominal and shoulder girdle. The use of these exercises not only improves

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pulmonary ventilation which is a vital point, but also gives the child a means within his own power for not only controlling his breathing but for relieving dyspnea. When one considers that dyspnea develops at approximately the point at which the lung ventilation has been reduced by one half, it is obvious that even a small increase in the aeration of the lungs may be followed by almost immediate relief of dyspnea. It is imperative that the exercises be done in a regular routine at the same time of day so that they may be learned so well as to become automatic and can be used when the child is having difficulty in breathing. This is a point which is difficult for parents to understand, since the concept that much of the difficulty in breathing is due to obstruction of the airway by secretions is one which is unfamiliar to them.

Most parents and many physicians think only of the use of bronchodilators in the medical treatment of attacks of asthma. These are of course vital and are the drugs indicated at the onset of an attack, but once the bronchodilator has exerted its effect, little more benefit can be obtained by repeating it. This undoubtedly accounts for much of the so-called "adrenalin-fastness." It is not that the adrenalin has failed to do its job as a bronchial dilator, but simply that it is not sufficient to produce an adequate airway. The steroids, as has been pointed out by many, are a double-edged sword in chronic asthma. Once they are started, it is extremely difficult to discontinue them. In our opinion, they have a place in the treatment of the acute life-threatening episodes of asthma. They offer certain hazards for prolonged use such as interference in growth. On numerous occasions in the past it has been our experience to have started a child with severe chronic asthma on steroids with the idea that we would produce a remission in which diagnostic studies, particularly skin testing, could be carried out. We found that following this procedure the patient was reluctant to discontinue the steroids so that in spite of carefully worked out programs to taper him off, the drug was continued far beyond the actual needs. It was usually continued in a fashion which we felt was not only ineffective but hazardous. We have seen instances in which children have suffered serious complications from steroids. The most alarming of these, pseudo–tumor cerebri has occurred in a few instances,[18] and growth arrest in many instances. Our thinking has taken on an even more somber aspect in regard to the use of steroids in chronically asthmatic children since we have had 5 sudden deaths in steroid-treated asthmatic children who had received the drug over long periods of time during the past 5 years. This is in contrast to 2 deaths in the previous 15 years, one of which was due to pneumonia with acute dilatation of the stomach as a complication of asthma and the other to pneumonia in a debilitated asthmatic baby. It perhaps is unfair to be too impressed with these hazards of steroid therapy in the chronically asthmatic child since in many instances they are life saving and life restoring. The tendency which parents have to abandon all other types of therapy which have ever been given to them and rush immediately to the use of steroids for each attack the child has is a trend which I think has been noted by many physicians recently. A survey of the use of steroids in patients referred to us for study of allergy in the past year showed that 25 per cent had received steroids before any attempt was made at specific treatment.[19] One can summarize the use of steroids by saying

that they are undoubtedly the most notable and the only truly new addition to our therapy of asthma in many decades. They introduced an entirely new concept into the treatment and in the mechanism of allergic reactions. They are the most potent, and the most potentially dangerous, of the drugs in our armamentarium. They unfortunately are used so often in such a casual way that their power is not fully appreciated by many physicians and certainly not by most patients.

Turning now to special facilities for the rehabilitation of asthmatic children we find that there are three well-established schools for them: The Jewish National Home for Asthmatic Children in Denver, Colorado; The National Foundation for Asthmatic Children in Tucson, Arizona; and the Betty Bacharach Home for Asthmatic Children in Longport, New Jersey. The total capacity of these three schools is approximately 200 patients. These institutions perform a notable and outstanding task of rehabilitating a child who is chronically asthmatic and who has failed to respond to therapy in his home environment. When one considers how many chronically asthmatic children there are in this country, it is obvious that facilities for 200 are grossly inadequate. The three institutions all have as a goal the integrated approach to the general well-being of the patient. The Denver group has the philosophy that asthma is so intimately bound up with family problems that "a parentectomy" is a vital part of treatment. This consists of removing the child from his home to a stable atmosphere where parent substitutes are warm and accepting, and the child is freed from emotional conflicts. The school in Tucson has the advantage of the dry warm climate which is beneficial to many individuals who do not tolerate cold temperature and high humidity. The Betty Bacharach Home was opened to asthmatics in 1958, so that they have no long-term follow-up as yet. From reports from Denver and Tucson it is seen that most of the children who are discharged from these institutions enjoy periods of freedom from asthma of varying length on their return to their home environment. This seems in part to be related to the length of the child's residence in the school and the degree of participation in psychiatric contact which the parents have.

There are localities where convalescent hospital or foster home care for asthmatics is available at a local level. These places are far less numerous than is desirable and this is an area which could be exploited if sufficient interest in the chronic asthmatic child could be aroused. There are many hospitals which are ideally set up for the care of chronically asthmatic children. There are many schools which could be utilized for this purpose. To my knowledge there are no special camps for asthmatic children such as are available in certain areas for the diabetic. This, too, is an area which needs further attention for the asthmatic child. In some situations the camps for crippled and handicapped children can be utilized for selected pulmonary cripples. In certain localities, for example, in Charleston, West Virginia, under Merle Scherr,[20] active rehabilitation programs are being carried out in connection with hospitals, allergy clinics, and Y.M.C.A. programs. Here group therapy with graded exercise and with a variety of corrective exercises is available. In most places, interested persons could be found who could carry on this type of work with the asthmatic child if they had sufficient education and if the need for their help were pointed out. In most cities

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there are practicing physical therapists connected with hospitals or in private practice who can give instruction in breathing exercises, in corrective posture exercises, postural drainage, and similar physical therapy. These persons are not utilized to any extent by the general medical public and in most instances parents are entirely unaware that they have a valuable adjunct to offer the asthmatic child. All of the specialized schools for asthma actually are accessible only to the child with the most severe asthma who has failed to respond to treatment at home. As stated before, the numbers benefiting are too few to approach a solution for the problem of rehabilitating even a small fraction of children with chronic asthma. It is for this reason that the evaluation of the child's situation and the means for combating the causes of his symptoms and their management on an individual basis are so vital.

In every instance, the expectation of cure which the patient and the parents have, and which the referring family physician or pediatrician has, is a factor of which the allergist should be aware in his management of the case. The child who is "brought in for skin tests," is one in whom there is frequently the greatest discrepancy between the expectation of a quick, easy, effortless "cure" or relief of symptoms on the part of the patient and the parents and the allergist's expectation of "cure," when he realizes the magnitude of the physical handicap and the multiplicity of the precipitating factors. It is only when the patient and physician can come to a clear understanding regarding these matters that the two can work together. It is extremely difficult for many parents to stick with any routine which represents drudgery for any prolonged period. Many of the things which an allergist recommends be avoided are things which interfere greatly with creature comforts enjoyed by the family. This represents a point of hostility and frustration which may serve as a stumbling block for carrying out other aspects of the program which would be of no inconvenience to anyone once they were established. These factors are often the ones which determine the success or the complete collapse of an allergy program. People's previous experience with allergy frequently colors their attitudes toward cooperation in the homework necessary in successfully managing the chronically asthmatic child.[21]

One additional point in the rehabilitation of an asthmatic child as he grows older is that of counseling regarding a suitable vocation. It is often inadvisable for a child who is allergic to have the contacts found on a farm or to continue in this type of environment. It is also unwise for many asthmatics to expose themselves to too strenuous exercise or to certain airborne irritants. It behooves the physician who is responsible for an adolescent with asthma to offer judicious suggestions and to be available for questions and advice regarding an occupation. There are many asthmatic individuals who could lead useful and economically productive lives had they been guided into fields which were compatible with their physical abilities. It is extremely important to start educating even the youngest child in the responsibility of caring for himself. All too often the sole initiative for relieving symptoms and for carrying out any prophylactic or preventive measures is either assumed by or dumped on the parent. This in time builds up resentment on the part of the parent and rebellion on the part of the

child when the parent in a dictatorial fashion suggests various measures which should or should not be done. If the child can be made to realize that it is he that has the illness and not someone else, that it is he who frequently holds the key to being sick or being well, then one can often make tremendous strides in general hygiene and health attitudes. This shift of responsibility is a useful device in combating the general overprotectiveness which the parents of the asthmatic child are apt to exhibit. The essence of rehabilitation of the child with asthma lies in educating him to an understanding of the mechanisms of his disease and the means of combating them, and of learning to make adjustments to live with them. This also involves education of the parents along the same lines, and also instilling in them an alertness and awareness that there are many things in our present-day complicated environment which are potentially unsuitable and poorly tolerated by an allergic individual.

The restoration of normal or nearly normal function in an allergic child, and the salvage of a pulmonary cripple to a productive life is a gratifying experience for all concerned. This could be done for many more children than are now helped by our limited facilities. If the various agencies who support rehabilitation programs for children could be convinced of the needs for help which the allergic child presents, and the reward in the restoration of a child who has no mental handicap in addition to the reversible physical problem, they could be of the greatest help to asthmatic children whose parents' means are overtaxed by chronic illness.

A cooperative effort which includes patient, parents, and physician, and extends to health officers and educators, social agencies, nutritionists, and physical therapists can bring the forgotten allergic child back to his place as a healthy useful member of society and prevent much illness and economic waste in later life.

SUMMARY AND CONCLUSIONS

1. Major allergy (particularly asthma, hay fever, and eczema) affects from 10 to 20 per cent of children.

2. Asthma killed 6,677 persons of all ages in the United States in 1957, of which 139 were children under 5, and 233 were under 19.

3. Acute poliomyelitis in this same period killed a total of 221 persons, of whom 53 were 5 years or under, and 119 were under 19 years.

4. The economic cost, the sickness days, the impaired efficiency due to allergy in the school child can only be surmised from the fact that 1 out of 3 children receives medical attention for allergy. Medication for allergy accounts for a large proportion of all drugs prescribed.

5. A sickness survey focused on allergic diseases and their antecedents, and the making of allergic diseases reportable to State Health Departments are two measures which should be instituted.

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6. There is a need for systematic individual medical programs and more numerous rehabilitation facilities for the child with chronic asthma.

7. Rehabilitation groups should be made aware of the magnitude of this problem of chronic asthma and their aid enlisted.

8. Education of patient, family, medical profession, and health organizations in the varied aspects of chronic allergy is urgently needed.

REFERENCES

1. Vital Statistics of the United States, U. S. Dept. of Health, Education, and Welfare, 1957, Vol. 2, Table 51.
2. Szanton, V. O., Rappaport, H. G., and Appel, S. J.: The Incidence of Allergy in a Pediatric Population Ann. Allergy **18**:45, 1960.
3. New Medical Marterial: Prescription Writing, Sept. 1959, p. 18.
4. New Medical Material: What Various Types of Hospitalized Illness Cost, p. 26.
5. Health Statistics, Disability Days, U. S. July 1957-June 1958. U. S. Dept. Health, Education, and Welfare. Series B-10, Table 31, p. 44.
6. Vital Statistics of the United States, U. S. Dept. of Health, Education, and Welfare, 1956, Vol. 2, Table 51.
7. Dees, S. C.: Development and Course of Asthma in Children, A.M.A. J. Dis. Child. **93**:228, 1957.
8. Glaser, J.: Allergy in Childhood, Springfield, Ill., 1956, Charles C. Thomas, Publisher, p. 7.
9. Kraepelien, S.: Personal communication to the author.
10. Abramson, H. A.: Evaluation of Maternal Rejection Theory in Allergy, Ann. Allergy **12**:129, 1954.
11. Cormia, F. E.: Basic Concepts in the Production and Management of the Psychosomatic Dermatoses, Brit. J. Dermat. **63**:83, 1951.
12. Wolff, H. G., Wolf, S. G., and Hare, C. C.: Life Stress and Bodily Disease, Baltimore, 1950, Williams & Wilkins Company.
13. Dees, S. C.: Inter-relationships of Allergic and Psychiatric Factors in Allergic Children, Proc. Twelfth Institute of Woods Schools, Nov. 1945.
14. Miller, H., and Baruch, D. W.: Psychosomatic Studies of Children With Allergic Manifestations. I: Maternal Rejection: A Study of Sixty-Three Cases, Psychosom. Med. **10**:275, 1948.
15. Baruch, D. W.: One Little Boy, New York, 1952, Julian Press.
16. Miller, H., and Baruch, D. W.: Some Paintings by Allergic Patients in Group Psychotherapy and Their Dynamic Implications in the Practice of Allergy, Internat. Arch. Allergy **1**:60, 1949.
17. Asthma Research Council, Kings College, London: Physical Exercises for Asthma, ed. 3, Chicago, Ill., 1939, Chicago Medical Book Co.
18. Dees, S. C., and McKay, H. W., Jr.: Occurrence of Pseudotumor Cerebri (Benign Intracranial Hypertension) During Treatment of Children With Asthma by Adrenal Steroids. Report of 3 Cases, Pediatrics, **23**:1143, 1959.
19. McKay, H. W., Jr., and Dees, S. C.: Experience With Adrenocorticosteroid Therapy in Allergic Children, North Carolina M. J. **20**:333, 1959.
20. Scherr, M. S., and Frankel, L.: Physical Conditioning Program for Asthmatic Children, J. A. M. A. **168**:1996, 1958.
21. Hogue, C. C.: Mother's Expectations of Cure in Pediatric Allergy Treatment at Duke University Medical Center, unpublished Masters Thesis, Duke University, 1959.

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NEUROLOGICAL DISEASES IN CHILDHOOD

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NEUROLOGICAL disease in childhood has been a long-neglected field in pediatrics. The neurologists have not understood children with such disease and the pediatrician's knowledge of neurology has been scanty. The result has been a long list of descriptions of hereditary degenerative diseases, named usually by the first describer, but still too little knowledge of how brain injury occurs in the fetus and newborn and of how growth and maturation affect the development of a damaged nervous system. The interest in this field, however, is increasing rapidly and intensive research is under way. Researchers are trying to find not only those metabolic disorders which cause mental deficiency, but also the effect of anoxia on the fetus and neonate.

Most of the children who have neurological disorders are among the cerebral palsied, the mentally retarded, and the epileptics. These three conditions vastly outnumber the hereditary degenerative diseases, and at present there is no indication that these conditions are on the decrease. On the contrary, it is more probable that the number will increase in the near future; many more prematures are saved now than even a decade ago, and antibiotics keep defective children alive much longer. The newer hazards of living include such things as head injuries from car accidents, and suffocation from skin diving and plastic bags.

There are severe gaps in our knowledge about what causes brain injury in fetuses and the newborn and of the seemingly random mechanisms by which anoxia damages the brain. Clinically, it is still impossible to predict at birth whether a child who has had a certain degree of anoxia will develop a particular kind of brain damage or indeed whether any brain damage will result. Some children develop spasticity, athetosis, or some other type of cerebral palsy, epilepsy with or without other neurological defects, or become mentally defective without motor involvement, while others are classified in a group now known to have organic brain damage without cerebral palsy or epilepsy.

*In the United States on Fulbright Travel Grant and One-Year (1958-1959) Study Grant from the American Association of University Women.

CHILDREN WITH ORGANIC BRAIN DAMAGE WITHOUT CEREBRAL PALSY OR EPILEPSY

This group now receives more recognition. These children have a short attention span, are often hyperactive, irritable, and difficult to discipline, have learning difficulties in perceptual areas, and are easily distracted. They cannot screen off unwanted incoming impulses, but have to react to everything which happens around them. Another characteristic is that they cannot see a whole situation; they concentrate on small details. It is important to recognize this group, because with right educational treatment they do better. Strauss and Lehtinen[1] have done pioneer work on this group of children.

CAUSES OF BRAIN INJURY

Practically all abnormalities or deviations during pregnancy and birth have been cited as the cause of brain damage in the child; some of these hypotheses have been proved, others are still conjectures.

The following are some brief comments and practical implications derived from our present knowledge. The literature in this field is overwhelming and will not be surveyed here. Most studies are retrospective, but certain figures are common to all of them and seem to be statistically significant.

That rubella in the mother in the first trimester has caused congenital defects seems to be proved, but it is less certain what other toxic agents may harm the fetus. Vitamin deficiency can cause malformations in animals,[2] but it is difficult to prove this in humans, and it is baffling that some children who have had all kinds of difficulty during fetal life are completely normal. It may be that the site of the implantation in utero and the functions of the placenta are not optimal in all cases and that this makes the difference in the ability of the fetus to withstand various stresses. Another theory is that not all neonates have brains of the same degree of maturation at birth.[3] In a study of 370 cerebral palsy cases[4] no more pregnancy disturbances were found than in the normal population, although in some of these cases the brain injury had obviously occurred before birth. Other workers have the same opinion.[5]

In Norway, almost half the cerebral palsy patients[4] had a difficult birth. On analyzing the pregnancies, prolonged birth was found to be the most common abnormality, with breech and foot presentation next. In another Norwegian survey from a district where practically all births were at a university clinic, there was no prolonged birth in the cerebral palsy cases; precipitate birth was the most common abnormality.[6]

Two causes of postnatal complication deserve consideration: kernicterus and upper respiratory infection in newborn infants. Kernicterus is not uncommon in premature neonates without any Rh or ABO incompatibility. Kell and other rare blood groups may cause sensitization. There have been several cases of kernicterus without demonstrable blood-group incompatibility between mother and child, even when testing was done with all the groups and subgroups known. All cases in which icterus appears on the first day of life* and all cases of icterus

**Editorial Note*—While there is correlation between the bilirubin and the probability of injury to the basal ganglia, the exact role of bilirubin is controversial.—*F.S.S.*

in premature neonates ought to be followed with bilirubin tests twice a day and treated with exchange transfusion if the bilirubin serum level rises above 18 to 20 mg. per cent.

A common cold in an infant may produce asphyxial attacks which can damage the brain. Respiratory distress must be regarded as a potential cause of brain damage throughout the newborn period, especially in premature neonates, whose respiration is often irregular. Close supervision of these children is necessary both day and night.

In meningitis cases, early diagnosis and treatment is of highest importance, to reduce the incidence of sequelae. Encephalitis, on the other hand, may be so mild that only the very observant mother and doctor can see something out of the ordinary when respiratory infections are present.

Accident prevention is a most important prophylactic measure. Thin plastic bags used for various commercial purposes have killed several babies. The bags develop static electricity, cling to the babies' faces, and suffocate them. They are very convenient as mattress covers, but highly dangerous as such and as toys.

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DIAGNOSIS OF BRAIN DAMAGE

Most important in the diagnosis of brain damage in infants and young children is to know how the normal child develops and what to expect of a child at different age levels. What is normal in a 3-month-old baby may be very abnormal in an 8-month-old baby. Without a thorough knowledge of normal infant development, it is impossible to diagnose anything except gross abnormalities in this age group. There are several excellent books on normal infant development, but the work of Gesell and his group[7] is best known.

The neurology of a developing nervous system is so different from that of the adult that there is need of a new nomenclature. There has been much discussion and misunderstanding because the terms from adult neurology have been used in child neurology with different meaning and interpretation. In some instances neurologists and pediatricians have not been on speaking terms. A workshop in London, 1958, tried to establish common ground and to define the terms used by the different clinicians; the conclusion was that they were discussing semantics.[8]

The technique of examining infants and small children neurologically is very different from an average examination of older children or adults. Small children usually do nothing on command, so that the secret lies in careful observation of the baby's own performance and, after the first two to three months, use of temping toys. In office practice it is a good idea to leave the child alone with some toys and to talk to the parents—the way a child plays may give useful information.

Normal children start playing very soon, and by watching the movements and the manner in which the child handles toys, good clues can be obtained as to coordination and developmental status. Wooden blocks, cars, dolls, small balls, etc., are tempting to most children. If the movements are clumsy when the child tries to grasp, this may indicate ataxia and athetosis. In testing, it is

better to let the child walk toward the mother, not from the mother to the doctor.

Our basis for understanding must begin with the reflex activity of the fetus and newborn. The work of Thomas and his collaborators[9] is fundamental. They have recorded a vast number of primitive reflexes in prematures and the newborn, as well as the age levels at which these reflexes disappear in normal infants. Usually, persistence of primitive reflexes beyond the physiologic age points toward mental deficiency and nonmaturation. The reflexes around the mouth, the grasping reflex in hands and toes, and the Moro embrace reflex are all easy to examine, and they give good clues.

CEREBRAL PALSY

Diagnosis and Treatment.—Early diagnosis and treatment of the child with brain injury is increasingly important. If cerebral palsy is diagnosed between the ages of 3 and 6 months and physical therapy is started, it is often possible to teach the child fairly normal movement patterns. There is evidence from experimentation in infant monkeys[10] that neighboring cortical areas can assume functions from ablated areas. With the motor cortex removed, infant monkeys grew up with normal movements; later, when the premotor cortex was removed, the animals lost voluntary movements. This leads to the hope that if infants are given enough stimulation to perform movements which are physiologic for their age, there may be movement patterns built up in areas adjacent to the injured ones.

Children with cerebral palsy lose a tremendous amount of kinesthetic and proprioceptive stimulation by not having normal infant movements. Some of this can be provided by treatment. The movements are done for the child several times each day by gently manipulating their arms and legs—lifting them up, curling them together, etc.—every time the child's diaper is changed or when the mother has time. The physiotherapist instructs the mother and asks for follow-up visits as often as possible; the doctor sees the child at least once a month. This has worked well in many cases.

The earliest clinical signs of cerebral palsy are, usually, deviation from normal in the tonus of the musculature and lack of spontaneous movements. These babies are more taut than normal. When they are lifted up by the hands, they do not reach a sitting position with the back curved; they often get to a standing position. The hands do not open and close spontaneously as do those of normal babies; it is often difficult to get a finger into the palms. Sometimes there is a little slough in the furrows of the hand, even in very well-tended, clean babies.

Most textbooks say that babies have their hands clenched up to 3 months of age. This is not true. Babies open and close their hands spontaneously from birth. This can be observed when the baby is relaxed. There is movement of one arm at a time, as well as of one leg, which may be a stretching or kicking movement. In some cases of cerebral palsy, the movements of the legs seem normal in the first months and the spastic stretch reflex is rarely seen until later—often not before 12 to 15 months. However, a certain stiffness, scarcity of movement, and adductor spasm in the hips may be present very early.

The athetoid baby often looks normal in the first months, if he does not have a very severe case in which feeding and respiratory difficulties may be present from birth. Moderate, mild athetosis is not seen until 8 to 10 months of age. The baby will not sit at the proper age and may be more limp than normal; he may have many movements, but will not start grasping at 3 to 5 months. A mother of an 8- to 9-month-old athetoid baby will often say, "He tries to grasp, but cannot make it." The movements are clumsy and look more like ataxic than athetoid movements.

Ataxia, which sometimes is more pronounced in the legs than arms, cannot be diagnosed with certainty until the child starts to walk; then it becomes evident in the unsteady gait. Usually, some incoordination in the use of hands and arms is also seen, but may be misinterpreted as clumsiness. Several of the children seen had difficult childhood and early school years because of unrecognized ataxia. With diagnosis and good physiotherapy these children can be helped considerably. In older children spasticity and athetosis are rarely missed these days; there is more question about the provision of the best treatment than about diagnosis, and this is still in the experimental stage. Different schools have different methods, but the stubbornness with which some treatment centers have defended their own methods seems to be declining. Good physiotherapy and orthopedic support is still the best treatment. It helps considerably in mild and moderate cases, although no one has yet shown remarkable results in cases of severe athetosis. The best hope for this pathetic group of human beings seems to be the development of neurosurgery. A few patients have been operated upon with remarkable results.

In severe spastic quadriplegia and hemiparesis, early treatment is all-important to the development of well-functioning hands. If physiotherapy and occupational therapy are started before one year of age and motivation geared to the child's developmental level, the chances for success are rather good. The hands have such wide areas of representation in the cortex that, if the physiologic age for development of hand movements is not missed, much can be done in rehabilitation which seems to carry over. If this period is missed, however, training of the hands is extremely difficult. The paretic arm and hand in a 5-year-old who has never used them are lost for practical purposes to everything except gross supporting movements. The legs and feet are more difficult to deal with; constant training is necessary.

Defects and Retardation.—In the group with brain injuries there are all kinds of defects—motor, sensory, hearing, speech, and visual—and many are mentally retarded. In the group of mentally retarded, more detailed examinations are necessary to find out whether this a partial defect which may necessitate special schooling, or whether it is generalized retardation. Reading difficulty may be a congenital defect or part of a more widespread brain injury, and it is found fairly often in the cerebral palsy group of children.

Perceptual difficulties in children with brain injuries are getting more recognition as diagnosis of them improves. Impulses must be transmitted to the brain from the sense organs before they can be elaborated and become knowledge. If the apparatus to deal with incoming impulses is defective, the facts

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become distorted. Gross visual defects and complete deafness have always been recognized and treated, but partial hearing defects are receiving more attention as knowledge of them increases. The Johns Hopkins group[11] has found central perceptual hearing defects in children who could hear slight sounds but who could not discriminate pitch. This condition must be differentiated from aphasia. Difficulties in form perception have been known a long time. They are common in children with injured brains and are relatively simple to diagnose with the aid of psychologic tests (Bender Gestalt, Goldstein, Scheerer, and others). Here, too, early training will save the children much worry and frustration in later school situations. If a child cannot discriminate between small differences in forms, he will have reading difficulties. There is no point in sending him to school if his perceptual ability has not developed to the necessary level.

Learning to Read and Write.—Mirror writing is more common in cerebral palsied children than in normal children, and is thought to be related to cerebral dominance. It has been found in a left-handed twin of monoovular twins with cerebral palsy.[12] Several cerebral palsied children have been found to have trouble in this direction with bilateral motor involvement—not only hemiparetics. In congenital hemiparesis, the dominance is probably placed in the normal hemisphere regardless of the side. New articles in this field appear constantly, and all point to the complexity of the problems. Each child has to be studied separately and treated according to his own abilities and shortcomings.

Motivation and Discipline.—A realistic handling of these children and their parents is of the highest importance and yet one of the most difficult problems in pediatric practice. Nowhere is there a greater territory for emotional turmoil than in these parents, and the right attitude in them is essential to the rehabilitation program for the child. It is the job of the doctor and social worker to have the parents and the child accept the truth and make the most of it. Hope for "a normal life" is unrealistic.

Most follow-up studies of adult cerebral palsy patients have shown that they are not well adjusted—emotionally, sexually, or in work.[13,14] More emphasis seems to be urgently needed on early psychologic help for the parents in handling the child.

SEIZURES AND EPILEPSY

Seizures are the most common occurrences in the field of child neurology and correct diagnosis and treatment are of highest importance. The first one or two seizures in a patient ought to be considered as a symptom not as a disease. Knowledge of which pathologic states or alterations of the physiologic states of the central nervous system can produce seizures is steadily increasing. Some factors which may alter susceptibility to convulsions follow:

Fever: Febrile convulsions are rather common in children, and decrease with age. After six years of age they are rare.

Blood sugar levels: Seizures from hypoglycemia are rare in children, but it is extremely important to diagnose them promptly since irreparable damage can result from a relatively short period of glucose deprivation in the brain.

Excessive hydration.

Pyridoxine deficiency: A relationship between pyridoxine deficiency and convulsive seizures has been established in experimental animals and in a few patients.[15,16] In a case of so-called B_6 dependency, in which the individual need for B_6 is greater than normal, the seizures stopped and the encephalogram became normal during intravenous injection of B_6.

Alkalosis and anoxia: Both can produce seizures.

Alterations in a number of ions, such as sodium, potassium and calcium: When a spike occurs, there is an increase of sodium and a decrease of potassium in the cell.

Some inborn errors of metabolism, as in phenylketonuria, and probably in Tay-Sachs disease, tuberous sclerosis, and others: These alter the metabolism of neurons and produce seizures in a way not yet understood.

Drug toxicity (convulsive drugs), infections of the nervous system, uremia, and hepatic coma.

Fatigue, inanition, emotional stress, boredom, inattention, drowsiness, endocrine alterations, and photic stimulation (some individuals convulse if subjected to flickering light).

What Is Epilepsy?—Epilepsy from an electrophysiologic viewpoint is a highly synchronous discharge and repetitive firing of many neuron elements. Why this happens is not yet fully understood, although much research is being conducted in this area. Studies by Lennox[17] suggest a hereditary susceptibility in certain individuals to react with seizures.

Epilepsy is seen in a much higher percentage of individuals with brain injury than in the rest of the population. In individuals with war injuries to the head, those with penetrating wounds had the highest percentage of post-traumatic epilepsy (40 to 50 per cent), with the highest incidence (65 per cent) when the damage was to the parietal lobe.[18]

In a survey at the University Clinic, Oslo, Norway, Eek and Skatvedt[19] found pathologic pneumoencephalograms in 60 per cent of 165 epileptic children (without cerebral palsy), and in 80 per cent of those in whom the seizures had started before 2 years of age. In 40 per cent of the cases where abnormal pneumoencephalograms were found, no etiological factor causing brain injury could be found. It has been claimed that children with cerebral palsy have as high as 47 per cent incidence of epilepsy[20,21]; other figures vary from 23.8 to 18 per cent.[4,5,22] All the authors agree that hemiparetics have the highest seizure frequency (35 to 43 per cent).

In terms of management, epilepsy is a chronic disease and should be treated as such. In children it is necessary that a long-term treatment program be carried out. Seizures from tetany and low blood calcium in the blood are rare, but must not be overlooked. The more rare, but very important, cases of hyperinsulin seizures in infants are even more necessary to detect. If the brain cells get insufficient glucose blood sugar for even a relatively short time, irreparable brain injury can follow.

In an average case of epilepsy the program should be as follows: A thorough examination of the child, including a neurological examination, should be made

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to exclude any of the nonepileptic causes of seizures. (Tumor of the brain with seizure as the first manifestation is not common in childhood; usually other neurological signs are the indicators of tumors.)

An electroencephalogram should be made in all epilepsy cases. This will give information as to the focus and demonstrate whether it is localized or widespread and whether the background activity is normal or dysrhythmic. It also shows whether there is a bilateral synchronous spike wave, and whether it is the three per second variety or more atypical.

The prognosis is different if the child has a small, localized focus in the posterior cortex or an atypical, bilateral, synchronous spike-wave pattern. The former has a good prognosis; the latter, a guarded one. Cortical foci are much easier to control with antiepileptic medication than are deep-seated foci, and may disappear. Migration of foci has been seen in children, and the prognosis in such cases seems to be good.[23,24]

Psychomotor epilepsy in its classic form, with dreamy states and bizarre behavior, is relatively rare in children. It is a question of semantics whether the frequent abdominal aurae noted in children are labeled psychomotor or autonomic. Abdominal discomfort as aura is frequent in children, and usually leads to grand mal seizures; in control with antiepileptic drugs it may persist as the only manifestation. Abdominal pain as the only manifestation of epilepsy is rare—Livingston[25] has seen only 20 cases in his vast experience.

Petit mal status is easily overlooked. The children who have petit mal attacks get more and more irritable, disobedient, and walk around in a dazed condition. One mother reported, "He works himself up to a good spanking." These children may be mistakenly referred to a child psychiatrist for behavior problems. Actually, treatment should be with antiepileptic drugs, not with psychotherapy or punishment.

Treatment of Epilepsy.—Most cases of childhood epilepsy can be controlled with drugs. The only problem is to find the best drug or combination of drugs in each case and to keep the child under supervision long enough. The most widely used drugs are phenobarbital and Dilantin—singly or in combination.

The author has seen very few adverse effects of phenobarbital when it is given at bedtime and in dosage rarely over 0.05 grams in children under 8 to 10 years of age. In many cases of grand mal, this is enough to control the seizures. If more is needed, Dilantin is the drug of choice and can be given two or three times a day. Mysoline has its use and may control seizures which have been refractory to the other drugs. If possible, only morning and evening doses are given; a midday dose is so much easier to forget and is more inconvenient for the children, especially if they are in school.

The Tridione group is used primarily in the control of the petit mal type of seizure. The myoclonic and akinetic types of seizure are much more difficult to control and are more often associated with severe brain injury than are other types. In these cases one has to try all the antiepileptic drugs individually and in combination. Often the effect is temporary, and one has to switch over to other drugs after some months or years.

Milontin and Celontin deserve a trial in some patients and are reported to be less toxic than the diones.

In those children who have infantile spasms which start after a few months of age and a hypsirhythmic electroencephalogram, ACTH is worth a trial. The etiology of these cases is still obscure, and everything ought to be tried. In this group of epileptic children, the prognosis is poor and most of them have, or develop, severe brain damage.

This is not a complete list of the treatment of epilepsy. It is meant only to be a general survey; for details and a complete list of antiepileptic drugs, the reader is referred to the textbooks on the subject. Generally, one starts with the most common and least toxic drugs in moderate doses, and works on from there. Frequent and long-lasting seizures do not always warrant large doses; sometimes severe grand mal seizures can be controlled completely with moderate medication of phenobarbital or Dilantin. Each case, however, has to be treated individually. According to Gibbs,[26] epilepsy in children ought to be controlled with modern medication in about 80 per cent of the cases.

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INBORN ERRORS OF METABOLISM

New familial diseases of the nervous system are being described, and there is beginning to be some understanding of the metabolic errors which are responsible for some of them. Those conditions in which metabolic error is found are disturbances in: amino acid metabolism (phenylketonuria, maple-sugar urine disease, H disease); carbohydrate metabolism (galactosemia); and pigment metabolism (congenital nonhemolytic jaundice with kernicterus). Newly described familial diseases with unknown etiology are ataxia telangiectasia,[27] and an unusual form of cerebellar ataxia with sex-linked inheritance.[28]

Phenylketonuria is well known as a cause of mental deficiency and patients with it often have seizures. It is caused by a familial-recessive gene and produces a deficiency in an enzyme system (that of phenylalanine hydroxylase, which converts phenylalanine to tyrosine), with an excessive accumulation of l-phenylalanine in blood and spinal fluid. The excessive phenylalanine is converted by its transaminase to phenylpyruvic acid which is then excreted through the urine. A new possibility to prevent clinical cases may be to find carriers by phenylalanine tolerance tests. There are also encouraging reports on the effects of phenylalanine-low diet if given from infancy.[29]

Maple-sugar urine disease was first described in 1954[30] as a progressive, familial, cerebral dysfunction associated with the presence of an unusual substance in the urine. At 3 to 5 days of age infants with this disease show symptoms of feeding difficulties, absence of Moro embrace reflex, and irregular, jerky respiration, followed by spasticity and opisthotonus. Convulsions and paralysis are often noted, and the infants die within a few weeks or months. This disease represents a defect in the branched-chain amino acids. Valine, leucine, and isoleucine are increased in blood and urine, and threonine, serine, and alanine are decreased. Diagnosis is made by paper chromatography by which increased amounts of the branched-chain amino acids in blood and urine can be demonstrated. So far, no therapy has been developed.

H disease was first described in 1956 by Baron and co-workers[31] as a disease characterized by a pellagra-like skin rash, neurological changes, cerebellar ataxia, and constant aminoaciduria. At times the patients have had coarse nystagmus, ptosis, increase of deep reflexes, tremor, mental deficiency, and spontaneous involuntary movements of the hands and tongue. The disease may be a disturbance in nicotinic acid metabolism, but therapeutic efforts in giving these patients nicotinic acid have not been of convincing value.

Of the known metabolic disturbances of carbohydrates, only galactosemia has some relation to childhood neurology, since children who survive without diagnosis are reported to be dwarfed at 2 to 3 months and cataracts and mental retardation may occur. When the condition is diagnosed and milk is removed from the diet in the first weeks of life, the development is normal.

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It is important that pediatricians be alerted to an error of pigment metabolism, congenital nonhemolytic jaundice with kernicterus, which has been described only in two families. It is a nonhemolytic jaundice with kernicterus manifested in the second day of life, with increase in the indirect bilirubin without hemolysis, and without group incompatibility. The parents show a decreased ability to form glucuronides following administration of salicylates and other metabolites. The infants show a marked inability to handle bilirubin, which can be discovered by bilirubin excretion test. The condition is probably transmitted by a single, autosomal recessive gene. Hsia[29] suggests that exchange transfusions be performed during the first weeks of life, when the brain is most susceptible to damage.

Idiopathic spontaneous hypoglycemia is probably a familial metabolic defect; early diagnosis is all important, since permanent brain damage with epileptic seizures and mental retardation results in the untreated severe cases. It appears usually before the age of 2 years and may be seen in infants. Neurological findings are those usual in the hypoglycemia of diabetics in insulin coma. The treatment is to give ACTH.

Ataxia telangiectasis is a familial disease whose main symptoms are a slowly progressing ataxia, progressive symmetrical scleral and cutaneous telangiectasia. and recurrent lung infections. This condition was first reported in 1941,[32] and about 20 cases have been reported since 1957—9 of which have been in southern California.[27] No treatment is known.

Another form of cerebellar ataxia with sex-linked inheritance was reported by Malamud and Cohen.[28] The initial cerebellar ataxia, dysarthria, and cerebellar signs were gradually replaced by extrapyramidal symptoms and seizures. Mental deterioration occurred in the cases.

The most recently described familial disease is cerebral palsy of the von Bogaert-Bertrans type, 8 cases of which have been reported in Jewish families.[32] This is a degenerative disease of the central nervous system and seems to be a defect in the water metabolism of the brain. Brain biopsy showed spongy edema of the lower cerebral cortex, Purkinje layer of cerebellum, subcortical white masses, severe lack of myelinated fibers, and presence of Alzheimer II glial cells. Clinically, there is bilateral spasticity, blindness, macrocephalia, and hypotonicity of cervical muscles. Treatment was attempted with urea as a dehydrating agent.

REFERENCES

1. Strauss, A. A., and Lehtinen, L. E.: Psychopathology and Education of the Brain-Injured Child, vol. I, New York, 1948, Grune & Stratton, Inc.
2. Wilson, J. G., and Barth, S.: Fetal Death and Maldevelopment Resulting From Maternal Vitamin A Deficiency in Rat, Proc. Soc. Exper. Biol. & Med. **72**:687, 1949.
3. Windle, William F., Editor: Neurological and Psychological Deficits of Asphyxia Neonatorum, Springfield, Ill., 1958, Charles C Thomas, Publisher.
4. Skatvedt, Marit: Cerebral Palsy. A Clinical Study of 370 Cases, Acta paediat. **46**: suppl. 111, 1958.
5. Asher, P., and Schonell, F. E.: A Survey of 400 Cases of Cerebral Palsy in Childhood, Arch. Dis. Child. **25**:360, 1950.
6. Hvidsten, J.: Cerebral Palsy Conference, Oslo, Norway, 1957. In press.
7. Gesell, A. L., and Ilg, F. L.: Infant and Child in the Culture of Today, New York and London, 1943, Harper & Brothers.
8. Cerebral Palsy Bulletin No. 5, Spring 1959.
9. Thomas, André: Etudes neurologiques sur le nouveaux-né et le nourrisson activité comparée des membres supérieurs et inférieurs, Encéphale **45**:101, 1956.
10. Kennard, Margaret: Reaction of Monkeys of Various Ages to Partial and Complete Decortication, J. Neuropath. & Exper. Neurol. **3**:289, 1944.
11. Hardy, William G.: Problems of Audition, Perception and Understanding, a keynote address at the 1956 Summer Meeting of the Alexander Graham Bell Association for the Deaf, in Los Angeles; Washington, D. C., The Volta Bureau.
12. Skatvedt, M., and Morley, D. E.: Cerebral Palsied Monoovular Twins, J. Speech & Hearing Disorders **22**:343, 1957.
13. Meyer, E., and Crothers, B.: Psychological and Physical Evaluation of Patients With Cerebral Palsy Studied for Periods of Ten Years or More, Am. J. Phys. Med. **32**:153, 1953.
14. Jones, Margaret H., and Maschmeyer, J. E.: Childhood Aims and Adult Accomplishments in Cerebral Palsy, Internat. Rec. Med. **171**:219, 1958.
15. Maloney, C. J., and Parmalee, A. H.: Convulsions in Young Infants as a Result of Pyridoxine (Vitamin B_6) Deficiency, J.A.M.A. **154**:405, 1954.
16. Hunt, A. D.: Abnormally High Pyridoxine Requirement. Summary of Evidence Suggesting Relation Between This Finding and Clinical Pyridoxine "Deficiency," Am. J. Clin. Nutrician **5**:561, 1957.
17. Lennox, W. G.: The Heredity of Eqilepsy as Told by Relations and Twins, J.A.M.A. **146**:529, 1951.
18. Kaplan, H.: Management of Craniocerebral Trauma and Its Relation to Subsequent Seizures, American Epilepsy Society Meeting, New York, Dec. 11, 1958.
19. Eek, S., Skatvedt, M., Gardborg, O.: Correlation Between Clinical and Pneumoencephalographic Findings in Epilepsy in Children, presented at Scandinavian Pediatric Congress, Helsinki, Finland, June 1958. In press.
20. Perlstein, M. A., Gibbs, E. L., and Gibbs, F. A.: The Electroencephalogram in Infantile Cerebral Palsy, Res. Publ., A. Nerv. & Ment. Dis. **26**:377, 1947.
21. Perlstein, M. A., Gibbs, E. L., and Gibbs, F. A.: The Electroencephalogram in Infantile Cerebral Palsy, Am. J. Phys. Med. **34**:477, 1955.
22. Brockway, A.: The Problem of the Spastic Child With a Clinical Summary of One Thousand Cases, J.A.M.A. **106**:1635, 1936.
23. Gibbs, E. L., Gillen, H. W., and Gibbs, F. A.: Disappearance and Migration of Epileptic Foci in Childhood, A.M.A. Am. J. Dis. Child. **88**:596, 1954.
24. Lundervold, A., and Skatvedt, M.: Migration of Spike Foci From One Hemisphere to the Other in Children, J. Pediat. **48**:457, 1956.
25. Livingston, S.: The Diagnosis and Treatment of Convulsive Disorders in Children, Springfield, Ill., 1954, Charles C Thomas Publisher.
26. Gibbs, F. A., and Stamps, F. W.: Epilepsy Handbook, Springfield, Ill., 1958, Charles C Thomas Publisher.
27. Boder, E., and Sedgwick, R.: Ataxia-Telangiectasia: A Familial Syndrome of Progressive Cerebellar Ataxia, Oculo-Cutaneous Telangiectasia, and Frequent Pulmonary Infection, U.S.C. M. Bull. **9**:15, 1957.
28. Malamud, N., and Cohen, P.: Unusual Form of Cerebellar Ataxia with Sex-linked Inheritance, Neurology **8**:261, 1958.
29. Hsia, David Yi-Yung: Inborn Errors of Metabolism, Chicago, 1959, Year Book Publishers, Inc., p. 112.
30. Menkes, J. H., Hurst, P. L., and Craig, J. M.: A New Syndrome: Progressive Familial Infantile Cerebral Dysfunction Associated With an Unusual Urinary Substance, Pediatrics **14**:462, 1954.
31. Baron, D. N., Dent, C. E., Harris, H., Hart, E. W., and Jepson, J. B.: Hereditary Pellagra-like Skin Rash With Temporary Cerebellar Ataxia, Constant Renal Amino-aciduria, and Other Bizarre Biochemical Features, Lancet **2**:421, 1956.
32. Zu Rhien, Gabriele M., Eichman, P. L., and Puletti, F.: Cerebral Palsy of von Bogaert-Bertrand Type: A Neuropathological and Clinical Description, reported at 11th Annual Meeting of American Academy of Neurology, Los Angeles, April 13 to 18, 1959.

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THE COMMUNITY AND THE MENTALLY RETARDED

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THERE is increasing interest among social workers, physicians, educators, and others in the provision of facilities for the mentally retarded within the community. In the past, when a physician was faced with advising a parent in regard to a mentally defective child he invariably advised placement in an institution.[1,2] It was the feeling that a child with much less than average understanding and intelligence would be an emotional and physical burden at home. The concern about the influence of defective children on siblings in the home was another factor that was responsible for this attitude. It has gradually become apparent, however, that institutional care for those with less than average intelligence is not the solution.

INSTITUTIONAL CARE

Parents who place their children in institutions continue to be emotionally upset because of guilt feelings about sending their child away.[3] This, in turn, does not help the emotional climate of the family and the other children may develop irrational fears based on placement of the defective child outside the home. Schipper,[4] in a study of Mongolism pointed out that normal siblings can adjust to such a child in the home with minimal adverse effects. When parents understand the needs of all the children and are realistic in their thinking about the retarded child, fewer negative reactions occur in the siblings.

Even if parents are willing to place their retarded child in an institution, the lack of facilities present a problem. It is estimated that 1 per cent of the population is severely defective mentally. In California with a population of 13,922,000 (July 1, 1957), 140,000 individuals might enter institutions for the mentally retarded if there were enough beds for them. Actually, there are a total of 11,334 beds in the six State Hospitals in California which provide care for the retarded. The cost of building new accomodations would amount to $7,500 per bed, with maintenance for each individual amounting to $2,500 per year.

Usually, institutions for the retarded are built far from centers of population. Our community conscience seems to be salved by providing custodial facilities where the physical needs of the retarded might be met. These buildings teem with patients who get a bare minimum of physical care and little else for the most part. There has, however, been an improvement in the care of these individuals in many States. In some, they are getting schooling within their ability to learn; the cerebral palsied are receiving therapy, and those with other handicaps are receiving specific help. However, the feeling of belonging to an intimate family group is missing and, as the individual gets older, there is diminishing contact with the family.

Recently a group of physicians from Southeast Asia visited this country for ideas about providing for the mentally retarded in their own country. With the improvement in public health techniques throughout the world, children are now surviving who in the past would have died, and many countries are now faced with the problem of caring for those who cannot care for themselves. When these visitors were shown our State Hospitals with their thousands of patients, they were appalled. They felt they could never herd people into such institutions and were determined to find some alternatives to the institutional care of the retarded.

The family of a retarded child can be assisted in the acceptance of the diagnosis of mental retardation by the physician. By emphasizing the values of the child a positive approach can be developed. It is also important for the doctor to "leave the door open" so that parents have someone to whom they can talk as the child grows and shows improvement or fails to improve. Many parents continue to "shop around" because of what seems to be a lack of interest on the part of the doctor. Rather than recommend institutional placement, the physician should be prepared to predict, as well as he can, the way in which the child will develop and the eventual intellectual potential that the child is likely to attain. With this information the family is in a better position to determine its own plans for the child. The question of institutional placement can be considered as well as other programs that may be available in the community. In any case, each child should be considered individually in relation to the family's own cultural and social background, religious attitudes, and all other factors that must be considered in relation to the handling of such a child.

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EDUCATION

In many communities nursery school programs are available now for the mentally retarded child. These have been started by parents of retarded children and serve in the preliminary preparation for socialization of these children. These centers are useful in the education of parents in regard to the problems of the retarded child and the family, and also provide opportunities for group therapy of the parents conducted by appropriate professional personnel.

When the child reaches the age that makes it possible for him to attend a special school, he can go on to the next phase in his training and education.

There have been public school programs for the retarded in California since 1921. The California State School Code has had a mandatory provision requiring

local school districts to provide educational facilities for the educable retarded child which generally includes children with an intelligence quotient between 50 and 70. More recently, the State School Code has included a provision which permits local school districts to set up training facilities for children who are considered trainable but not educable; these are generally the children with intelligence quotients below 50. For this group the school program[5] is directed toward the formation of good habits for daily living and socialization.

At school the retarded child attains an education within his ability to learn and receives training in everyday living. His family has the satisfaction of knowing that for several hours of each weekday he is occupied, during which time the family is able to carry on a fairly normal existence.

But what happens when the school program is completed? Many remain at home and do what they can about the house; some become delinquent because of little to do with their time; others end up in a State Hospital when the family is unable to carry on with their supervision. Some communities are beginning to make attempts to meet the problem of the older mentally retarded individual by providing training in order to make these individuals more useful and productive citizens.

Davies[6] points out that "of the current trends in preparing retarded young people for a useful place in the world, three seem of special promise: more attention to personality; more realistic training in public schools and institutions; greater cooperation between schools, institutions, training and placing institutions." An impetus to the training of the mentally retarded occurred in 1943 with the enactment of Public Law 113 which made it possible for the Office of Vocational Rehabilitation of the Federal Security Agency to offer vocational training and placement for mental defectives through its local branches. Further aid became possible through the enactment of Public Law 565 in 1954 providing for the expansion of sheltered workshops for the retarded and for the development of special demonstration projects. The following will relate the development of such a program in San Francisco with the aid of funds from the Office of Vocational Rehabilitation.

A sheltered Workshop was started originally in 1951 as an activity of Aid to Retarded Children, Incorporated, of San Francisco (ARC), oriented to the employment of the most severely retarded "unemployable" individuals in order to provide supervised training at minimally complex activities. With the development of case work services and psychological evaluation procedures, a wider variety of activities was offered. It became apparent that many who had been previously considered beyond help began to show promise. It was found that the sheltered workshop could provide a realistic service to the more able retarded individuals in terms of work habits, work skills, evaluation, and training. The staff began to devise and experiment with methods, and observe the factors of work adjustment and the skills involved in a variety of employment areas. As the project developed, it was aimed at demonstrating how vocational rehabilitation services could be effectively provided in a work training center for the mentally retarded.

VOCATIONAL REHABILITATION

A grant was obtained from the Office of Vocational Rehabilitation, U.S. Department of Health, Education, and Welfare, for a demonstration project to apply in the Work-Training Center the knowledge and procedures which had been learned from other agencies with similar objectives, to increase substantially the number of previously unemployable retarded adults for remunerative employment, to strengthen and increase statewide and local services and facilities for the vocational rehabilitation of the severely handicapped mentally retarded

TABLE I. DISTRIBUTION OF IQ SCORES OF ENROLLEES IN WORK-TRAINING CENTER, JUNE 1, 1959*

IQ	MALE	FEMALE	TOTAL
85+	0	1	1
80–84	0	2	2
75–79	2	0	2
70–74	2	2	4
65–69	6	1	7
60–64	3	3	6
55–59	4	3	7
50–54	4	4	8
45–49	3	2	5
40–44	4	3	7
35–39	3	0	3
30–34	2	3	5
25–29	1	3	4
Below 25	1	0	1
Total	35	27	62

*The mean IQ for the group of enrollees in the Work-Training Center on June 1, 1959, was 52.5. Only 9 out of the total of 62 had an IQ of 70 or more.

adult, and to integrate the services of voluntary agencies and governmental programs to achieve these aims. It was also hoped that experience would make it possible to define and to develop the major factors to promote success in the vocational rehabilitation of mentally retarded adults.

As the program developed three major administrative divisions evolved: rehabilitation services; production; clerical services.

Rehabilitation Services.—The rehabilitation services of the Work-Training Center include social services, psychological services, work evaluation, vocational guidance and counseling, vocational training, job placement, and follow-up after placement.

Social Services.—The social worker is a key person in the program; her background and training are essential in dealing with the client and his family, in understanding their many problems, and in working closely with other agencies and other organizations in the community which may be involved.

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A group therapy program has been developed by the Chief Social Worker. At a weekly meeting the participants discuss some of their mutual problems as unemployed adults such as: a projection of their own hostility toward the world upon what seems to be a hostile employer who refuses to hire them; unrealistic evaluation of the relationships between employer and employee; fantasy concerning abilities and limitations; inaccurate self-concepts; confusion concerning their own views and station in life vs. their parents' views; devaluation of their own capability; and fear of work outside the sheltered situation.

Psychological Services.—The greatest emphasis has been directed toward the development of the evaluation program and provision for training, therapy, and research.

Guidance.—In order to plan a suitable training and vocational program, it is imperative to have some knowledge of the intellectual and emotional functioning of the client and an assessment of academic achievement, occupational skills, work potential, and individual work habits.

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TABLE II. MEDICAL PROBLEMS AFFECTING THE 62 WORK-TRAINING ENROLLEES IN ADDITION TO MENTAL RETARDATION, JUNE 1, 1959

Cardiac	2
Cerebral palsy	10
Convulsive	8
Dental problems, severe	3
Diabetes	2
Emotional	25
Hearing loss, severe	2
Hydrocephalus, arrested	1
Microcephaly	1
Mongolism	5
Paresis, general	1
Poliomyelitis	1
Encephalitis sequelae	3
Sarcoma	1
Spinal fusion	1
Ulcer, peptic	1
Visual problems, significant	3

Each enrollee in the Center is exposed to standardized psychological tests which include the Wechsler Adult Intelligence Scale, the Rorschach, the Thematic Apperception Test, the Wide Range Achievement Test, and the Bender Visual Motor Gestalt Test.

As one would expect, there are a significant number of problems associated with brain damage (Table II): 10 of the enrollees had evidence of cerebral palsy of a mild to a moderate degree; a history of convulsions or a diagnosis of convulsive equivalent was made in 8 cases; 3 individuals had significant visual problems; and 2 had severe hearing loss. These disturbances complicated further the training of the affected individuals and added to the handicap presented by the

mental retardation. In some cases more than one associated handicap was present, (for example, cerebral palsy and convulsions).

Emotional disturbances occurred in 25 of the enrollees and were severe enough to influence their adjustment to the program and to their preparation for a vocation. It was evident that the emotional problem in some cases was the determining factor which prevented the individual from becoming independent. Some histories suggested that the retarded individual was made more dependent by his family than was necessary. It is possible that the overprotection resulted from feelings of guilt on the part of the parents and caused them to make up to their child for his limitations, thereby making him more dependent than the facts warranted.

Dr. Lawson G. Lowrey,[7] a former Director of the Institute for Child Guidance in New York City explained the behavior tendencies of the mentally deficient in terms of "a conflict over difference or, if one prefers the term, inferiority complex." In attempting to compensate for his intellectual limitations which cause him to fail in competition, the deficient child may demonstrate difficult behavior. Dr. Lowrey further states that such mechanisms are not confined to the mentally deficient but occur in children of average or superior intelligence and result from difficulties such as physical handicaps, home difficulties, or sense of social inferiority. He concluded "that intelligence is only one of the many factors which may produce objectionable reactions and that factors of personality, the integration of the emotional and instinctive life, and in the social situation are far more important than the mere question of intelligence."

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Table II also indicates the etiological factors responsible for the mental retardation in some of the cases. The largest single cause was Mongolism (5); 3 patients had a history of encephalitis, 1 had arrested hydrocephalus, 1 microcephaly, and 1 general paresis.

Assessment of Occupational Skills and Work Potential.—Two basic occupational areas have been established at the Center: manual dexterity and basic clerical skills. In all activities a specific number of objects must be handled and the score is based on the total time required to complete the assignment. Manual dexterity work samples include folding, sorting, assembling, racking, and packaging. Clerical work includes stapling, inserting addressed printed material into envelopes, filing, counting, and money handling.

A third occupational area—proficiency with tools—is measured by the Tweezer Dexterity Test and the Hand-Tool Dexterity Test.

Training.—Some of the contract work received at the Work-Training Center between Nov. 1, 1957, through June 1, 1959, included the following: affixing glued stickers; assembling chains; box making; brush packing; Christmas wreath decorating; cleaning, counting, and packing awl handles; cleaning and repacking leather cutters; collating and stapling; counting and boxing tack pullers; counting, inserting, and tucking tissues; counting and packing heel tips; counting and tying leather thongs; correcting printing errors; cutting and winding ribbon; foam rubber bagging; folding belt box and inserting plastic cover; folding, inserting, sealing, and stamping mailers; folding and sealing envelopes; index card stapling;

labeling and packing; labeling, sorting, and boxing belts; manufacturing bait boxes; manufacturing Christmas tree stands; modifying kit bags; modifying straps; newspaper processing; packing gun patches; packaging dye kits; pen assembling; pen filler packaging; pen nib counting and packing; removing and replacing fillers; rubber stamping envelopes; stapling envelope tags; sorting, bundling, and mailing magazines; tag cord tying; and unstuffing envelopes. In addition to such contract work, training has been carried on by performance on the job at the Workshop as messenger, clerical worker, vendor's stand attendant, porter, teacher's helper, and kitchen worker.

Job Placement.—The success of a vocational training program is measured by the ability of the enrollees to obtain employment. During the period between Nov. 1, 1957, and May 30, 1959, 21 enrollees of the Worker-Training Center were either on temporary placement in the community or on field training assignment in jobs ranging in length of employment from 2 hours to 8 months. The following types of work were represented: dishwasher, furniture mover, laundry helper, nurse's aid, porter, patcher (rubber), painter, general laborer, trucker, helper, stockman, and commissary worker. All of the trainees were highly motivated in their approach to these employment experiences and reports on their performance were most satisfactory. All the trainees tried hard to please; some improved their skills on the job. The cooperation of the employers was excellent—they understood the limitations of these people and worked closely with the Vocational Counsellor.

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SUMMARY

The attitude of community management of the mentally retarded is changing. It is no longer the universal attitude that retarded individuals should necessarily be placed in institutions. There is a growing awareness that for many families the presence of a retarded child in the home is not an insurmountable catastrophe. Parents of these children have been pioneers in community projects which make it possible for the retarded to remain at home and to adjust socially to those around them.

The gaps in community resources are being filled, and although school programs have been available for a long time it is only recently that there have been provisions for the preschool child. Most important, sheltered workshops and vocational training centers are being developed to provide opportunities for the retarded person who is no longer in school in order to develop skills and a vocation which might make him independent and a contributor to society.

The development of a community program based on family unity and furnishing facilities to develop the maximum potential in the retarded individual not only provides economic advantages for some but also adds to the dignity of man.

I wish to thank Dr. Elias Katz, Director, and Mrs. Myra Schapps, Chief, Social Services of the Work-Training Center of Aid to Retarded Children, Inc., San Francisco, California, for their information in relation to the activities of the Work-Training Center.

REFERENCES

1. Aldrich, C. A.: Preventive Medicine and Mongolism, Am. J. Ment. Deficiency **52**:127, 1947.
2. Editor's Column: Early Home Care or Institution for the Retarded Child, J. Pediat. **42**:396, 1953.
3. Kirman, B. H.: Mongolism: Diagnosis and Management at Home, M. World **78**:258, 1953.
4. Schipper, M. T.: The Child With Mongolism in the Home, Pediatrics **24**:132, 1959.
5. Laws and Regulations Relating to Education and Health Services for Exceptional Children in California, Calif. State Dept. Education, 1954, Education Code Sec. 980.
6. Davies, S. P.: The Mentally Retarded in Society, New York, 1959, Columbia University Press.
7. Lowrey, L. G.: *In* Davies, S. P.: The Mentally Retarded in Society, New York, 1959, Columbia University Press, p. 99.

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INFECTIONS IN THE NEWBORN PERIOD

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THE leading problems in the care of the newborn today are prematurity, congenital anomalies, the respiratory distress syndrome, and infection. Great efforts are being made in many quarters to enhance understanding of the causes of prematurity and of congenital anomalies. Decrease in mortality and morbidity in these two important areas concerning the newborn will undoubtedly depend more on prevention than improved therapy. Understanding of the physiology and pathogenesis of respiratory distress has been rapidly growing, but it has not reached the point where precise, effective, and rational therapy can be applied to the sick infant. In the field of newborn infection on the other hand, especially bacterial infection, there are available a great variety of antibiotics. Early recognition of infection, correct identification of the infecting organism, and the proper choice of antibiotic therapy may prove life saving to the infant. The focus of this paper will be primarily with these aspects of newborn infection.

EARLY RECOGNITION OF INFECTION

Sepsis in the newborn runs a rapid course; mechanisms of host resistance are incompletely developed and many of the conventional signs of infection, such as fever and leukocytosis, are often absent; this is particularly true in the case of the premature. Therefore, in order to recognize infection early enough for effective treatment, a high degree of suspicion and constant vigilance are necessary. Vigilance should start before the infant is born—the presence or suspicion of maternal infection or of premature rupture of amniotic membranes should alert one to the possibility of infection in the newborn. One should not wait for the appearance of frank clinical signs, but every effort should be made to confirm suspicion and to establish the nature of the infecting organism as early as possible. Culture of the maternal amniotic fluid at the time of delivery is very helpful. Alternatively, one might aspirate gastric contents immediately after birth, make a Gram stain of a smear, and take a culture. The presence of microorganisms on the smear is very suggestive of aspiration of infected amniotic

fluid and possible impending bacterial infection, especially pneumonitis. Another recently described technique is to section and examine the umbilical cord at the time of delivery.[1]

Once the baby is placed in the newborn nursery, the physician and nurse must watch for minor signs of infection. Fever is often absent. When present it may be due to dehydration or the weather rather than infection, but elevation of temperature in the newborn should not be discarded lightly as a warning sign. Jaundice is a common sign of infection. "Jaundice rounds" at the beginning of each nursing shift are a very helpful routine in the newborn nursery. That the baby is "not doing well" in the opinion of an experienced nursery nurse often is the most helpful sign of all. A white blood cell count is worth doing; leukocytosis is often absent in the septic newborn, but is significant when present. Examination of the urine and spinal fluid may help in identifying the organism. Blood cultures are very important if suspicion of newborn sepsis exists.

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THE STAPHYLOCOCCAL PROBLEM

In the past few years considerable world-wide attention has been given to the problem of staphylococcal outbreaks in newborn nurseries and to the particular importance of a few phage types of staphylococci, notably the 80/81 strain, in causing these outbreaks. The problem of impetigo and other staphylococcal infections in the newborn nurseries is not new, of course. The reason for the increased attention is that the introduction of phage typing in recent years has enabled us to trace the spread of specific and epidemic strains in the nursery.

Hurst[2] and Gillespie[3] have studied the colonization of various body sites of the clinically well newborn. Their studies suggest that when a newborn baby enters the nursery, many areas of the body may become colonized with staphylococci. The rate and extent of colonization depends on many factors; among these are the prevalent strain of staphylococcus in the nursery, the degree of care employed in nursing techniques, and the use of antiseptic compounds on the skin. Many other factors are undoubtedly also involved, but the relative importance of these is not entirely clear. The preponderance of evidence suggests that the principal source of spread of staphylococci are the older, already colonized infants rather than personnel carriers. These observations suggest that there might be some advantage in delaying heavy colonization in the newborn nursery, thus permitting the baby to acquire the household strain of staphylococcus instead of that prevalent in the nursery. Good nursery technique, and the use of antiseptics on skin and cord are all directed to this end.

It is quite common to have heavy colonization of almost all infants and yet very little disease,[3] so that it may not always be apparent to the nursery personnel what the true incidence of infection is. The median time of appearance of disease in the baby is 7 to 8 days of age, which almost always finds the baby at home. In order to keep a constant check on the state of infection in the nursery it is necessary, therefore, to have a method available for checking on the babies at home. This may be done by means of postcard or telephone survey, by seeing the babies in a well-baby clinic, or by keeping in touch with physicians who will see the infants in their offices.

Another interesting aspect of staphylococcal infections in the newborn is the very frequent spread of infection to other family members and the great length of time over which these family infections may persist. In a recent study[4] we surveyed 94 families whose infants were in the newborn nursery during an epidemic situation 15 months previously. Approximately 40 per cent of the families had experienced some infectious disease—infant infection was most common, maternal infection second in frequency, followed by sibling infection, with the father as the least often affected member. The majority of infections involved the skin and caused more discomfort than harm. There are other occasional serious and even fatal infections within the family group such as osteomyelitis and staphylococcal pneumonia. In our experience efforts in eradicating the staphylococcus in affected families, particularly those with many children, have proved difficult and have met with little success.

The *management* of staphylococcal infections in the newborn involves year-round vigilance in the newborn nursery and constant attention to technique, handling of an epidemic if it occurs, and management of the individual infected baby.

Much has been written on nursery technique. The American Academy of Pediatrics[5] has an excellent manual as a guide to the operation of nurseries. The important factors are individual handling of babies, strict aseptic technique between infants, and infinite attention to minutiae. So many factors have been implicated in outbreaks (oxygen outlets, rectal thermometers, improper handling of linen, air circulation vents) that nursery routines need constant scrutiny. Personnel who have frank staphylococcal infections which are shedding organisms should not be allowed in the nursery. It seems unreasonable, however, to exclude all carriers of either coagulase-positive staphylococci or of any particular strains, since in due time a significant number of the personnel would be expected to acquire the prevalent organism. The Committee on Fetus and Newborn of the Academy of Pediatrics has recommended the use of pHisoHex on the skin and triple dye on the cord of the newborn. It seems reasonable to use some non-irritating antiseptic agent, and there may be other useful ones.

In handling an epidemic in the nursery, the first step is to impose rigid technique and to isolate the newly arriving susceptible babies from the older and potentially infected babies. One ought next to conduct an inquiry into the possible causes of the outbreak; this should include a review of techniques as well as survey of personnel. Infection may be introduced from other areas of the hospital and this should be looked into. Shaffer[6] has used erythromycin very successfully to stop an epidemic situation in the nursery.

The three principles of management of the individual baby are supportive care, incision and drainage of pus where it is present, and the intelligent use of antibiotics.

OTHER BACTERIAL INFECTIONS

The most serious threat to any newborn baby is generalized septicemia. This is a serious generalized infection involving the blood stream and many organs, and often complicated by meningeal infection. Smith[7] has recently written

a comprehensive review of this problem. The organisms most commonly involved are *Staphylococcus aureus* and the enteric group of bacteria; the beta streptotoccus and enterococcus are less common invaders. The presence of infection is insidious and difficult to recognize with certainty. Fever, although often absent in the newborn in the presence of infection, is an important sign if it is present. Anorexia, jaundice, omphalitis, convulsions, fullness of the fontanelle, and hepatomegaly are other signs which may be present. The observation by an experienced nurse that an infant is "not doing well" is extremely helpful before the frank clinical signs develop. Leukocytosis may or may not be found, but the white blood count is well worth obtaining. Anemia may be present, and there may be pus in the urinary sediment. Lumbar puncture may yield pus or the causative organism. When suspicion of generalized sepsis exists, it is most important to obtain a blood culture before proceeding with antibiotic therapy.

Another important bacterial infection in the newborn is epidemic diarrhea caused by enteropathogenic *Escherichia coli.*[8] Certain serotypes of *E. coli* have been implicated within recent years as etiological agents of infantile diarrhea. It is important to recognize this fact and to look for enteropathogens, which are distinguishable from other coliform organisms only by serotyping. Stulberg and co-workers[9] have been able to demonstrate, in one epidemic caused by the $0{:}127B_8$ strain, that there was no associated cytopathogenic agent. Enteropathogenic *E. coli* have a high degree of susceptibility to neomycin, which is the drug of choice for this infection.

Salmonella infection is relatively uncommon but has been implicated in several serious nursery outbreaks.[10] This infection is usually characterized by blood or mucus in the stool; diarrhea may be absent. Watt and co-authors[11] have described a detailed epidemiologic study of such an outbreak in a premature nursery. Presence of this infection can be detected by culturing abnormal-appearing stools. Its prevention and control depend ultimately on the excellence of nursing techniques, particularly handwashing.

Pseudomonas pyocyanea infection is becoming more frequent in the newborn nursery. Propagation is enhanced by the humid, warm environment of the incubators. Pseudomonas is also a common superinfecting organism in a newborn who is receiving antibiotics. The emergence of this pathogen might serve as a warning that strict adherence to asepsis is needed in the nursery rather than more and better antibiotics.

MONILIA INFECTIONS

The appearance of thrush in the mouth of newborns is not uncommon and as long as the lesion is limited to the mouth, it seems to be harmless to the individual baby. The diagnosis can be made clinically by inspection and confirmed by demonstrating Monilia in the lesions. A significant proportion of infected babies harbor the fungus in their intestines and develop an unpleasant diaper rash.[12] Kozinn[13] has demonstrated the origin of cutaneous moniliasis from intestinal tract infection. This bright red rash in the diaper area, particularly around the rectum, is resistant to conventional therapy. Monilia can be demon-

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strated in smear or culture. It is more common to find cutaneous moniliasis in slightly older infants, but it may also be seen in the newborn nursery. Moniliasis also occurs as a superinfection in antibiotic-treated infants. Occasionally debilitated or premature infants may acquire pulmonary moniliasis as a complication. Such an infection is very serious and may prove fatal. Nystatin, which is the drug of choice in monilial infection, is not absorbed from the gastrointestinal tract and thus is of little use in systemic moniliasis.

There is excellent evidence that Monilia infection of the infant is acquired from the maternal vagina probably in the course of labor and delivery.[14] Subsequent spread may occur on a wide scale within the nursery, propagated by the nurses' hands, nursing bottles, etc.[15] Prevention of Monilia infection thus depends on case finding and therapy of maternal vaginal moniliasis prior to delivery and on excellent nursery technique. Therapy of known maternal vaginal moniliasis is important, therefore, in prevention of this infection.

Therapy of oral thrush is not difficult. Mechanical removal of the white patches with a cotton tip is important. Several agents are satisfactory; among them are nystatin, 25 per cent sodium borate in glycerine, and gentian violet. The latter has the disadvantage of an unpleasant violet stain on linen which will not washout. Nystatin is the drug of choice for gastrointestinal and cutaneous moniliasis.

VIRAL INFECTIONS

Until the recent advances in tissue-culture methods, little was known about viral infections in the newborn. Much still remains to be learned, but several important facts have been established.

The newborn may be colonized and excrete a great variety of viruses without evidence of clinical infection. Moscovici and co-workers[16] reported on the isolation of viruses from 52 healthy newborn babies; predominant was the ECHO virus group. This group of viruses is not always innocuous for the newborn, however. Eichenwald[17] has reported an outbreak of epidemic diarrhea due to ECHO virus, type 18. Respiratory illness apparently caused by ECHO viruses has also been reported,[18] as has respiratory disease associated with adenoviruses and hemadsorption viruses in influenza.

A number of reports from this country and abroad have implicated Coxsackie viruses, group B, as a cause of serious, often fatal, disease in infancy. Kibrick[19] has recently reviewed some of these reports. Most of the illnesses occurred early in life; myocarditis and meningoencephalitis were the two primary manifestations, but other organs were also involved. The virus was isolated from feces, brain, spinal cord, myocardium, and liver. There is very good evidence that two of these infants acquired the virus in utero.

Cytomegalic inclusion disease has become more and more frequently recognized in the very young infant. This disease is not uniformly fatal. A wide variety of organs are involved; the infants exhibit jaundice, petechiae, hepatosplenomegaly, and hemolytic anemia. There are many neurological manifestations, the

most important of which is perhaps chorioretinitis, which has to be distinguished from chorioretinitis produced by toxoplasmosis. Characteristic inclusion bodies have been demonstrated in urinary sediment, in ventricular fluid, and in gastric washings.[20,21] Salivary gland virus has been isolated in many patients with cytomegalic inclusion disease and is probably the etiological agent in this disease.[21]

Many other viral infections have been demonstrated in this period of life and the possibility of viral causation must be kept in mind in all illnesses in the nursery. At present there is no specific therapy for these infections, but it is important to learn to recognize these clinical entities and to try to confirm their presence in the laboratory.

RATIONAL CHOICE OF ANTIBIOTICS

The cardinal principle in the intelligent use of antibiotics is to ascertain the infecting microorganism and then to choose the appropriate antibiotic. In the case of the newborn and, particularly of the premature, it is often difficult to do this. The difficulty of recognizing infection and the rapid progress of infection because of inadequate host defense usually demand that antibiotic therapy be started before a possitive culture report can be obtained. At this point the best possible educated guess of the most probable infecting organism must be made and therapy directed against that organism. We have already stressed the importance of obtaining all possible clues and cultures prior to or at the time of delivery. When infection is suspected, blood cultures and cultures of the infected site must be promptly obtained so that antibiotic therapy which has been started in the meantime may be appropriately changed when the organism is determined.

PROPHYLACTIC USE OF ANTIBIOTICS

There is probably no justification in the prophylactic use of any antibiotic in uninfected newborn babies. It has been demonstrated repeatedly that infection can be acquired while antibiotics are being given; their routine use certainly introduces additional problems in the care of the newborn. Their usefulness in preventing hospital-acquired infection is sharply limited by the fact that many organisms prevalent in the nursery would in time become resistant to all the commonly used antibiotics. This is certainly true of many strains of *Staph. Aureus.* Where there is good reason to believe that the baby has had significant exposure to infection, however, it may be well to treat the infant for a few days with an agent which seems appropriate for the probable pathogen. Such a patient is the baby whose mother has had ruptured membranes for more than 24 hours or known antenatal maternal infection, or the premature infant born without aseptic precautions or transported without asepsis. The choice of antibiotic should be such as to be adequate to deal with the two most common pathogens, *E. coli* and *Staph. aureus.* It must also have no appreciable toxicity for the baby. In the case of known infection it is permissible to risk toxicity in choosing the most effective drug, but when the antibiotic is to be used prophylactically one must be particularly careful to avoid possible harm to the infant.

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THERAPEUTIC USE OF ANTIBIOTICS

Usually the problem is one of selecting the best drug or drugs for a baby who is suspected of having sepsis, but where the organism is not yet known. At the present time there is no drug or combination of drugs which is ideally suited for this purpose.

Because of poor host defense one should attempt to use a bacteriocidal rather than a bacteriostatic agent. Among these are penicillin, streptomycin, polymyxin B, bacitracin, and neomycin. Penicillin is still a most useful drug; it is bacteriocidal and has no demonstrated toxicity in the newborn. Its usefulness as a single drug, however, is sharply limited by the facts that it is not very effective against *E. coli* and that a very high proportion of hospital-acquired strains of *Staph. aureus* are penicillin-resistant. Streptomycin is effective against *E. coli* and may also be effective against some strains of *Staph. aureus*. The combination of penicillin and streptomycin which is so frequently employed is rather useful, but will fail in a significant portion of the hospital strains of staphylococci which are resistant to both penicillin and streptomycin. The other bacteriocidal agents listed all share a certain degree of toxicity, and for that reason should not be used until it is known that they would be effective against the infecting microorganism. Once identification is accomplished, however, they have a real value in therapy.

The bacteriostatic drugs are the tetracyclines, chloramphenicol, erythromycin, ristocetin, novobiocin, and the sulfonamides.

Despite its demonstrated occasional depression of the bone marrow, chloramphenicol has seemed until recently to be the most useful single drug in the newborn. It is effective against *E. coli*, most hospital strains of staphylococci, and many other microorganisms; it is available in a variety of forms for oral, intravenous, or intramuscular use. The recent demonstration of its toxicity and hazards in the premature,[22] however, has called for much more caution in its use. It probably should not be used prophylactically; there is no need to hesitate to use it therapeutically, but determination of blood levels probably could be made to make its use safe (a relatively easy colorimetric method has been made available by Parke, Davis and Company).

The members of the tetracycline group of drugs are bacteriostatic and have the disadvantage of encouraging superinfection. Most hospital strains of staphylococci are resistant to these antibiotics.

Erythromycin is a most useful drug in dealing with Gram-positive cocci but is totally without merit for *E. coli* and, for that reason, it probably should not be used alone in infections of undetermined causation in the newborn.

The use of novobiocin is limited to treatment of resistant staphylococcal infections. It should be used in combination with other drugs in order to delay emergence of resistant strains; it may produce toxic side effects.

Kanamycin is pharmacologically almost indistinguishable from neomycin and its toxicity is similar. Agents such as vancomycin and ristocetin have an added limitation in the newborn because they can be administered only by the intravenous route. Silverman's[23] demonstration of the toxicity of sulfisoxazole

(Gantrisin) in the premature has sharply limited the use of sulfonamides in the newborn. Nystatin is useful in monilial infections of the gastrointestinal tract, but is not systemically absorbed and is not helpful in monilial pulmonary infections.

The dosages of antibiotics in the newborn have been empirical over the years and little is known about the ability of the newborn to metabolize and excrete most of these drugs. Recent work with chloramphenicol has accentuated the limitation of knowledge in this respect. Good data are becoming available for blood levels of chloramphenicol in the newborn and similar data are needed for many other antibiotics. As a guide to dosage, Kempe's[24] recent article provides a table of antibiotic dosages for children, but these are only roughly applicable to the newborn.

The means of administration of antibiotics deserves careful consideration. A very ill newborn may not absorb well from the gastrointestinal tract. A small premature, however, may be seriously traumatized by repeated venipunctures. Thus, the route has to be individualized.

Although the treatment of infections of unknown causation has been stressed, I would like to emphasize that once the organism is isolated more precise antibiotic selection should be made. It is well to be aware of the current sensitivity pattern of prevalent hospital microorganisms. Disc sensitivity tests can give a rapid, rough guide to useful antibiotics. A more precise but somewhat more time-consuming method of determining tube sensitivity[25] might be employed. This is particularly useful in suggesting effective combinations of antimicrobial agents and differentiating bacteriocidal from bacteriostatic combinations of drugs.

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SUMMARY

A brief review of some of the problems of infection in the newborn has been presented. Emphasis is placed on a high level of suspicion of sepsis and an aggressive effort to identify the infecting organism. These efforts should start in the delivery room, or even before, in order to initiate timely and rational therapy. Selection of the most appropriate antibiotic is made difficult by the frequent necessity of prescribing therapy before the identity of the infecting organism is established. Possible toxic effects of the drugs used in therapy must be kept in mind.

Colonization of the newborn occurs early and the spread is probably from the older infants in the nursery to the new arrivals. When infectious strains become established in the newborn, his entire family may later be plagued with unpleasant staphylococcal infections which stubbornly resist eradication.

The possibility of viral infections in the newborn must be borne in mind. Knowledge in this field is just developing, but several definite clinical entities have been recognized.

REFERENCES

1. Benirschke, K., and Clifford, S. H.: Intrauterine Bacterial Infection of the Newborn Infant, J. Pediat. **54**:11, 1959.

2. Hurst, V.: Transmission of Hospital Staphylococci Among Newborn Infants. II. Colonization of the Infant Skin and Mucous Membranes, Pediatrics **25**:204, 1960.
3. Gillespie, W. A., Simpson, K., and Tozer, R. C.: Staphylococcal Infection in a Maternity Hospital. Epidemiology and Control, Lancet **2**:1075, 1958.
4. Hurst, V., and Grossman, M.: The Hospital Nursery as a Source of Staphylococcal Infection in Families of Newborn Infants, New England J. Med. **262**:951, 1960.
5. Academy of Pediatrics: Standards and Recommendations for Hospital Care of Newborn Infants—Full-Term and Premature, Evanston, Ill., 1957.
6. Shaffer, T. E., Baldwin, J. N., Rheins, M. S., and Sylvester, R. F.: Staphylococcal Infections in Newborn Infants. I. Study of Epidemic Among Infants and Nursing Mothers, Pediatrics **18**:750, 1956.
7. Smith, R. T., Platou, E. S., and Good, R. A.: Septicemia of the Newborn. Current Status of the Problem, Pediatrics **17**:549, 1956.
8. Cooper, M. L., Walters, E. W., and Keller, H. M.: Escherichia Coli Associated With Infantile Diarrhea, Ann. New York Acad. Sc. **66**:78, 1956.
9. Stulberg, C. S., Zuelzer, W. W., and Page, R.: Epidemic of Diarrhea of the Newborn—Nonassociation of Cytopathogenic Agents, A.M.A. J. Dis. Child. **95**:30, 1958.
10. Szanton, V. L.: Epidemic Salmonellosis. A 30-Month Study of 80 Cases of Salmonella Oranienburg Infection, Pediatrics **20**:794, 1957.
11. Watt, J., Wegman, M. E., Brown, O. W., Schliessmann, D. J., Maupin, E., and Hemphill, E. C.: Salmonellosis in a Premature Nursery Unaccompanied by Diarrheal Disease, Pediatrics **22**:689, 1958.
12. Bound, J. P.: Thrush Napkin Rashes, Brit. M. J. **1**:782, 1956.
13. Kozinn, P. J., Taschdjian, C. L., Dragutsky, D., and Minsky, A.: Cutaneous Candidiasis in Early Infancy and Childhood, Pediatrics **20**:827, 1957.
14. Kozinn, P. J., Taschdjian, C. L., and Wiener, H.: Incidence and Pathogenesis of Neonatal Candidiasis, Pediatrics **21**:421, 1958.
15. Ludlam, G. B., and Henderson, J. L.: Neonatal Thrush in a Maternity Hospital, Lancet **1**:64, 1942.
16. Moscovici, C., Ginevri, A., and Kempe, C. H.: The Distribution of Poliomyelitis and ECHO Viruses in a Children's Institution, A.M.A. J. Dis. Child. **98**:139, 1959.
17. Eichenwald, H. F., Ababio, A., Arky, A. M., and Hartman, A. P.: Epidemic Diarrhea in Premature and Older Infants Caused by ECHO Virus Type 18, J.A.M.A. **166**:1563, 1958.
18. Cramblett, H. G., Rosen, L., Parrott, R. H., Bell, J. A., Huebner, R. J., and McCullough, N. B.: Respiratory Illness in Six Infants Infected With a Newly Recognized ECHO Virus, Pediatrics **21**:168, 1958.
19. Kibrick, S., and Benirschke, K.: Servere Generalized Disease (Encephalohepatomyocarditis) Occurring in the Newborn Period and Due to Infection With Coxsackie Virus, Group B. Evidence of Intrauterine Infection With This Agent, Pediatrics **22**:857, 1958.
20. Blanc, W. A.: Cytologic Diagnosis of Cytomegalic Inclusion Disease in Gastric Washings, Am. J. Clin. Path. **28**:46, 1957.
21. Weller, T. H., Macauley, J. C., Craig, J. M., and Wirth, P.: Isolation of Intranuclear Inclusion Producing Agents From Infants With Illnesses Resembling Cytomegalic Inclusion Disease, Proc. Soc. Exper. Biol. & Med. **94**:4, 1957.
22. Sutherland, J. M.: Fatal Cardiovascular Collapse of Infants Receiving Large Amounts of Chloramphenicol, A.M.A. J. Dis. Child **97**:761, 1959.
23. Silverman, W. A., Anderson, D. H., Blanc, W. A., and Crozier, D. N.: A Difference in Mortality Rate And Incidence of Kernicterus Among Premature Infants Allotted to Two Prophylactic Antibacterial Regimens, Pediatrics **18**:614, 1956.
24. Kempe, C. H.: A Rational Approach to Antibiotic Therapy of Childhood Infections, Postgrad. Med. **24**:325, 1958.
25. Jawetz, E., Gunnison, J. B., Coleman, V. R., and Kempe, C. H.: A Laboratory Test for Bacterial Sensitivity to Combinations of Antibiotics, Am. J. Clin. Path. **25**:1016, 1955.

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MALIGNANT DISEASE IN CHILDREN

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MALIGNANT disease is a leading cause of death in children between the ages of 1 and 15 years, according to the mortality statistics of the United States for 1947.[1] Each year, approximately 4,000 deaths in children result from neoplastic diseases. Since the advent of antibiotics and the control of infectious diseases, more deaths in the childrens hospitals are due to malignant disease than to any other cause, except accidents. The time between the ages of 1 and 4 years is a relatively hazardous period in regard to malignancy. This is because of the occurrence of leukemia and tumors of embryonic origin, such as embryomas of the kidney, neuroblastomas of the adrenal medulla, retinoblastomas, and teratomas.[2]

Malignant tumors probably represent a heterogeneous group of diseases characterized by uncontrolled disturbances in proliferation and maturation of certain tissue cells. Current research has expanded our concepts as to the etiology and pathogenesis of cancer and leukemias. Ideas of single causative factors and abrupt and dramatic neoplastic transformation have been replaced by the concept that the neoplastic transformation of cells is a stepwise process from metaplasia and premalignant change to frank malignancy characterized by invasiveness and metastasis.[3] Neoplastic diseases are looked upon as having a natural history which may occupy a varying, often prolonged, period of time before the overt clinical manifestations of malignancy occur.

The interesting concept of host dependency of neoplasms, which has been developed from studies in animal endocrine organs, may have application to the interpretation of the clinical behavior of certain tumors in children. Dependent or host-conditioned tumors are those which are proliferating because of an alteration of the environment in which they grow and not because of a basic neoplastic change in the cell itself. If the environment is corrected, the neoplastic stimulus is removed and the tumor may regress.[4]

Autonomous tumors are those in which the neoplastic stimulus arises from within the tumor cells themselves, which have lost the capacity to respond to restraining factors in the host. There is probably no clear demarcation between

dependent and autonomous neoplasms, and tumors may show progression from dependency to autonomy spontaneously or as a result of radiation or chemotherapy. The spontaneous regression of neuroblastomas, in which differentiation occurs toward the histologically more mature ganglioneuroma, may represent an example of a host-dependent neoplasm which has been influenced by the changing physiologic environment of the growing child.[5] Similar regressions have been reported to occur spontaneously in other neoplasms in children, such as retinoblastoma, multiple papillomatosis of the larynx, and, transiently, in acute leukemia.[6-8]

As a result of the concept of the natural history of neoplasms, extended epidemiologic research is being conducted in an attempt to identify various agent, host, and environmental factors of importance in cancer. In this manner it is hoped to determine the relationship to cancer of such factors as race, sex, geography, socioeconomic status, nutrition, infectious disease, exposure to toxic agents, drugs, antibiotics, and genetic influences, among others. With knowledge of a few key factors in the natural history of the more common neoplastic diseases, preventive measures might be developed before the etiology and mechanism of carcinogenesis are discovered.[3]

It is of importance in the diagnosis of cancer in children to recognize that the most common sites of malignancy differ from those of the adult. In children, the kidney, the adrenals, the blood-forming organs, the bones, the central nervous system, and the supporting connective tissues are the most common sites of origin; whereas in the adult the gastrointestinal tract, the oropharynx, the genital organs, the respiratory system, the urinary tract, the breast, and the skin are the most frequent sites.

Other features of childhood neoplasms are of interest. Most malignant tumors of children grow rapidly, and metastasize or extend directly to the surrounding tissues early. Slow, lingering deaths which produce marked cachexia are not the rule since intercurrent infections or metastases to vital areas usually result in early death. Symptoms are produced usually from the effect of local tissue impairment, and pain is usually not prominent until the tumor mass is apparent. Pallor, anorexia, fever, weight loss, cough, constipation, hematuria, dysuria, vomiting, and irritability may be encountered, but these signs and findings are not diagnostic of cancer. Usually the single most valuable finding is an unexplained tumor mass.[9] A cardinal rule of cancer diagnosis is to consider any unexplained solid mass as caused by neoplasm until proper steps have been taken to rule out this possibility. Histologic examination of the entire mass, or a suitable portion, is essential for diagnosis. Surgical exploration may be necessary to accomplish this in intrathoracic and intra-abdominal tumor masses.

The remainder of this discussion will be devoted to a review of the most significant features of those childhood neoplasms which have the potential for cure or for significant palliation. These include neuroblastoma of the adrenal, embryoma of the kidney (Wilms' tumor), retinoblastoma, and acute leukemia.

Neuroblastoma.—This is a tumor of the sympathetic nervous system consisting of immature or undifferentiated neuroblasts. A ganglioneuroma is a tumor of well-differentiated nerve cells and nerve fibers. Gradations between the

immature cells of the former and the differentiated cells of the latter tumors can be found in many neuroblastomas. Neuroblastoma is most frequently found in the adrenal glands and, less often, in the ganglia of the sympathetic nervous system in the retroperitoneal area and in the posterior mediastinum. It rarely occurs in the central nervous system.[10]

Neuroblastoma is found predominantly in infants and children (about 20 per cent of the cases of cancer of children), with the majority of cases occurring within the first 5 years of life (about one-half during the first 2 years). Rarely, the tumor may be present at birth. Probably because of its slow growth rate, ganglioneuroma is more frequently seen in adolescence or young adult life. There is no sex, familial, or racial prediliction in the occurrence of neuroblastoma.[11]

The etiological factors are unknown. Neuroblastoma appears to develop from undifferentiated proliferating neural tissue from the adrenal medulla or the sympathetic nervous system and may arise as a result of a disturbance in the orderly processes of embryonic differentiation. Progressive differentiation of neuroblastoma to ganglioneuroma has been reported to occur on rare occasions, and neuroblastoma has been reported to undergo spontaneous remission.[12] These observations suggest that host-dependent factors may play a role in the natural history of this tumor.

A neuroblastoma grows rapidly; grossly, it is often soft and hemorrhagic, white or yellow in color, with necrotic and hemorrhagic foci, and may be lobulated. Microscopically, it consists of undifferentiated small round cells resembling lymphocytes with scanty cytoplasm and a few imperfect ganglion cells and fibrils. The fibrils are often arranged in longitudinal bundles or masses, in which groups of neuroblasts are found in characteristic clusters called rosettes. A ganglioneuroma is composed of adult nerve cells and nerve fibers. A neuroblastoma grows rapidly to relatively large size and metastasizes readily by the blood stream and by lymphatics. In the so-called Pepper type, there is frequent metastasis to the regional lymph nodes and to the liver with resultant progressive hepatomegaly and abdominal distention. In the Hutchison type, there are conspicuous metastases to the bones, especially to the skull, orbit, and the long bones. Involvement of the cranial orbit may lead to proptosis of the eye.

In neuroblastoma the most frequent finding is that of an abdominal mass without symptoms. Occasionally, bone metastases which result in bone pain may be the first manifestation. With the occurrence of metastases there may be fever, pain, swelling, evidence of nervous system damage, and the patient may appear chronically ill and pale. Orbital skull metastases produce ecchymoses of the lid, exophthalmos, and papilledema. The absence of hypertension in a patient with retroperitoneal tumor may help to differentiate clinically neuroblastoma from a Wilms' tumor.

Characteristic radiologic findings are often seen.[13] A mass can be visualized in the region of the adrenal by means of a flat film of the abdomen. Calcifications in the form of flocculent central deposits are seen in about half of the patients. The kidney may be displaced in any direction, but cranial or medial displacement is rare. Because these tumors arise outside of the kidney, renal function is not impaired on the involved side, although the pelvis and calices may be distorted

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and the renal configuration may resemble Wilms' tumor. Metastases to the skull, long bones, pelvis, and meninges are common. Typical bone lesions consist of small osteolytic defects and periosteal elevations. In advanced cases, pulmonary metastases may be present.

Laboratory findings are not characteristic. Anemia, leukopenia, and thrombocytopenia occur in the presence of bone metastases, and the tumor can be diagnosed occasionally by bone marrow aspiration biopsy. The sedimentation rate may be elevated. The absence of hematuria may assist in differentiation of neuroblastoma from Wilms' tumor. The diagnosis of neuroblastoma can be established only by biopsy; surgical exploration of the abdomen or thorax may be required for definitive pathologic diagnosis of the early lesion. The clinical differential diagnosis includes Wilms' tumor, retroperitoneal teratoma, hydronephrosis, renal cyst, pancreatic cysts, and psoas abscess.

At present, surgery is the treatment of choice for cure of the localized nonmetastatic neuroblastoma. When possible, the tumor is completely excised. If this is not possible the bulk of the tumor is resected, and followed with intensive irradiation therapy of the tumor bed.[14] When metastases are present, palliative treatment in the form of local radiation to bone lesions and soft tissue masses is given as necessary, in order to control symptoms of pain and pressure.

Chemotherapy has been disappointing in the control of neuroblastoma although rare responses to the antifolic acid drugs are noted. Recently, Bodian[11] reported dramatic results in disseminated neuroblastoma, excluding those patients with bone metastases, with the administration of massive doses of vitamin B_{12} over prolonged periods. The dose employed was 1 mg. intramuscularly on alternate days in infants under 1 year of age, and 0.14 mg. per kilogram on alternate days in older children. In children under 1 year of age Bodian obtained beneficial results, with infrequent responses in children over 1 year of age. These results are dramatic and require confirmation. It should be noted, however, that the best results from surgery and radiation therapy are also obtained in infants under 2 years of age,[15] suggesting that the tumor-host relationship may be of a different nature in the infant than in older children. With advanced disease, the prognosis is uniformly poor and relatively few patients survive for more than 1 year.

Nephroblastoma (Wilms' tumor, Embryoma).—Renal tumors of childhood are congenital and are believed to arise from embryonic cell rests consisting of immature renal cell tissue. Most pathologists believe that embryomas represent a neoplastic exaggeration of the normal developmental processes in the growth zones of the renal cortex in late fetal life or shortly after birth.[16]

Nephroblastoma occurs most frequently in children in the first 3 years of life, with the majority under 5 years and rarely in adults. There is no sex, familial, or racial predeliction. Nephroblastoma is usually single and unilateral but, occasionally, may be bilateral. The tumor is usually a well-delineated, encapsulated globular mass which appears on gross examination to be contiguous with the kidney. On section it is gray or grayish white in color, hemorrhagic, and necrotic. The histologic appearance is variable. Most of these tumors show embryonic renal tissue with varying degrees of differentiation, including primitive

renal blastoma, epithelial structures such as renal tubules, and glomeruli in all stages of development. Metastases occur most frequently by invasion of the renal veins to the lungs and brain; often, the tumor may invade the adrenals, liver, and intestines. Bone is practically never invaded, and this is an important differentiating feature from neuroblastoma.

Clinically, nephroblastoma usually has an insidious, painless onset and is recognized by the presence of a tumor mass. Pain may develop as the capsule and nerves are involved. Malaise, pallor, anorexia, and weight loss may occur. Fever is found in about one-half of the cases. Hypertension may be present in Wilms' tumor, but is not seen in neuroblastoma. Hematuria occurs in about 10 per cent of patients. Despite the occurrence of extensive pulmonary metastases, dyspnea is a late manifestation. Isolated varicocele may be present when the spermatic vein is compressed by the tumor.

Physical findings consist of an abdominal mass in the region of the kidneys which often may be quite large. It is usually firm and irregular and, deep in the abdomen, may displace the large bowel and diaphragm, and occasionally may be pulsatile due to vascularity. Ascites is infrequent.

Radiologic examination on a flat film of the abdomen reveals a soft tissue mass which displaces the intestines. Calcification is less frequent than in neuroblastoma but, when present, is characteristically distributed in a linear peripheral fashion, as compared with the central flocculant calcifications found in neuroblastoma.[13] The normal renal contour is usually deformed by the tumor, and the intravenous pyelogram may show distortion of the calices and pelvis. The dye is usually seen in the affected kidney. Pulmonary metastases are seen easily on chest films.

Diagnosis must be made by histologic examination and, frequently, surgical exploration is required for the evaluation of intra-abdominal tumor masses.

Treatment of nephroblastoma has varied considerably, with much discussion regarding the sequence of surgical and radiologic therapy.[17,18] Currently, it is believed that the most successful method is the combination of preoperative radiation, nephrectomy, and postoperative radiation. In a survey of the literature, Abeshouse[18] found that the 2-year survival of all reported patients thus treated was 25.8 per cent as opposed to a 15.2 per cent 2-year survival for patients who underwent nephrectomy and postoperative radiation. In patients with metastases, radiation therapy is used for palliation since these tumors are often extremely radiosensitive. Chemotherapy, in the form of an alkylating agent such as nitrogen mustard may, rarely, produce dramatic symptomatic and objective tumor regression for a brief period of time.

Retinoblastoma.—Retinoblastoma[16] is a congenital malignant tumor which arises from the nucleal layers of the retina as proliferation of the retinoblasts. Microscopically, it resembles neuroblastoma and medulloblastoma. This tumor is very uncommon; about 100 cases a year are reported in the United States, of which one-third are bilateral.

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Retinoblastoma is considered to have a genetic basis, as indicated by the strong family predisposition; however, a large percentage do not have any family history. The tumor predisposition is inherited as a dominant trait but, often, with incomplete penetrance. This results in several types of inheritance: (1) direct from an affected parent; (2) family showing affected siblings with unaffected parents; and (3) affected siblings, unaffected parents, but with affected aunts and uncles.[21] The disease is rare among the siblings of affected children, but extremely common in children born of affected parents. Such persons should be advised against having offspring.

Clinically, retinoblastoma becomes evident within the first years of life, the average age being 2 years, but it has been reported in a 1-month-old infant and in an 11-year-old child. There is no sex predeliction. The tumor may extend into the vitreous cavity of the eye or may invade the choroid and the optic nerve. In advanced states it may metastasize by the blood to distant organs such as bone, liver, and lymph nodes.

Early diagnosis may be difficult, since the tumor is most common in infants and may not be detected until a squint or signs of visual impairment are noted by the parents. Diagnosis is based on the finding of a white pupillary reflex, inequality in pupil size, and loss of vision in the affected eye. Retinoscopic examination reveals a tumor arising from the retina which may fill the vitreous cavity. Usually the tumor is pinkish or creamy in color and reveals newly formed blood vessels over its surface. An important diagnostic feature is the presence of whitish, sharply demarcated, calcified foci in the tumor which may also be demonstrated by x-ray.

When only one eye is involved, the other eye should be periodically examined, since one-third of the patients eventually develop tumor in the other eye.

The most significant features to influence the prognosis are the extent of the lesion and whether or not it is bilateral. When the tumor is confined to one eye and does not involve the optic nerve, enucleation results in a 50 per cent rate of cure. This figure is obtained in patients with bilateral disease in the absence of optic nerve invasion. Often parents refuse bilateral enucleation. In these patients, the eye showing the most advanced tumor is removed and careful irradiation therapy is given to the remaining eye. However, the amount of radiation required to cause the tumor to regress invariably produces secondary changes in the eye, so that vision is eventually lost. Recently, a dramatic improvement in the prognosis of inoperable retinoblastoma has been achieved by means of combination chemotherapy with triethylene melamine (TEM) and radiation therapy.[21] When TEM is given in conjunction with a course of irradiation therapy, a striking increase in cure rate is achieved with much less irradiation. Recent publications by Reese[19] indicate a 90 per cent cure rate.

Leukemia.[22-23]—Leukemia is a relatively uncommon disease, causing approximately 7 deaths per million population per year. It is, however, the most common single form of malignant disease in children and is responsible for about one-half of all deaths in children. Most leukemias in children are of the acute form and are predominantly lymphocytic in type. Chronic leukemia, lymphosarcoma, and Hodgkin's disease are relatively rare in children under 10 years of age.

During the past 20 years there has been a steadily increasing incidence of leukemia, amounting to approximately 5 per cent per year, with the highest incidence in the countries with the highest standard of living, for example, the United States, Denmark, and Great Britain. In the United States, the incidence curve shows a peak at 3 to 4 years which, interestingly, is confined to white children. Negro children do not show this peak. The general increase in leukemia has been attributed to many factors, despite the lack of information as to the cause of the disease. These factors include ionizing radiations, natural and medical, which have been implicated in about 10 to 15 per cent of cases. Stewart[24] found a significant increase of leukemia in children born of mothers who had received diagnostic x-ray pelvimetry during the prenatal period. Her findings are the subject of continuing investigation, but it is a reasonable policy for obstetricians and pediatricians to avoid unnecessary radiation exposure of the fetus and children.[22]

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The possible etiological factors in the remaining cases of leukemia have not been identified, but it has been suggested that they may lie in the ecologic environment to which modern man is subjected. Such factors include the changing dietary habits, food additives, use of vitamins and hormones, drugs, antibiotics, suppression of the normal immune responses by means of antibiotics, socioeconomic factors, and such environmental factors as geography, temperature, and altitude. Burnet has recently reviewed this subject in a most provocative manner and has stressed the need for intensive investigations in this area in an attempt to discover a means of preventing the occurrence of leukemia.

The diagnosis of acute leukemia in children is usually not a difficult one and the clinical course is fairly uniform.[25] Most patients have varying degrees of general symptoms such as malaise, loss of appetite, fatigue, weakness, fever, and weight loss. Early in the illness, the symptoms and findings are related to the involvement of the blood-forming organs and the lymphatic tissue, and produce symptoms and findings related to lymphadenopathy, splenomegaly bone pain, and tenderness. At this time the leukocyte count may be elevated, normal, or subnormal and always contains some abnormal, immature blast forms. Anemia is common and arises from replacement of normal bone marrow and from peripheral hemolysis. Occasionally, an intractable hemolytic anemia may precede the development of acute leukemia. The tendency to bleed, ranging from easy bruisability and epistaxis to petechiae occurs in association with thrombocytopenia. Symptoms of pressure may be produced by lymphadenopathy, particularly in the mediastinum, and later abdominal distention may result from enlargement of the spleen and liver.

The bone marrow aspirate typically shows the normal tissue to have been replaced with blast forms. It has been observed that the infiltration of the marrow by leukemic cells is often accompanied by markedly elevated intramedullary bone marrow pressures. This factor, in conjunction with periosteal infiltration, may account for the bone pain, tenderness, and arthralgia frequently seen in leukemic children.

In the later stages of leukemia, the impairment of such organs as the liver, kidneys, central nervous system, etc., contributes to the symptoms and findings.

An increase in intracranial complications in acute leukemia in children has been noted since the advent of chemotherapy and the occurrence of prolonged survival in many patients.[27,28]

The diagnosis of acute leukemia is relatively easy and is based upon the clinical features of lymphadenopathy, splenomegaly, evidence of a hemorrhagic diathesis, anemia, and the presence of abnormal leukocytes in the blood or bone marrow. It must be distinguished from infectious mononucleosis and infectious leukocytosis. It has been demonstrated recently that the classification of leukemic blast cells as to morphologic type is of value in determining the prognosis with the various types of chemotherapeutic agents. Patients with lymphoblastic leukemia have shown excellent initial responses to adrenal cortical hormones and antimetabolite therapy, whereas those with myeloblastic and monocytic leukemia do not respond to any great degree.[29]

The condition of the untreated patient usually deteriorates progressively with death eventually due to widespread hemorrhage and generalized sepsis. Spontaneous remissions of varying degrees have been reported in 7 to 10 per cent of untreated patients. These are usually of approximately 6 weeks in duration and are often preceded by infections and other forms of stressful illness. The addition of chemotherapy to the supportive care with antibiotics and blood transfusion has added important additional months of comfortable life to most children with acute leukemia. At present the survival time of 50 per cent of patients has been increased from 6 to 12 months, although other studies do not demonstrate this degree of benefit.[25,30]

As a result of intensive clinical and laboratory investigation, many new chemotherapeutic agents are anticipated within the next few years which may be of value in childhood leukemia. At present, the agents of proved practical value are the adrenal cortical steroids, the antifolic acid drugs aminopterin and methotrexate, and the antipurine drug, 6-mercaptopurine. It is customary to employ the adrenal cortical steroids in case of the symptomatic and acutely ill child until a remission is induced. Customary doses range from 30 to 100 mg. of prednisone per day. With the inception of a remission, the patient is begun on daily maintenance therapy with methotrexate, 2.5 to 5 mg., orally, daily until relapse occurs. At this time, the drug is discontinued and 6-mercaptopurine, 3 mg. per kilogram per day, is administered until a second relapse occurs. Adrenal steroids can be used at any time when there is acute systemic toxicity or in the event of the occurrence of hemolytic anemia. The oral mucosa should be examined carefully during treatment with the antimetabolite drugs for the development of shallow ulcerations which are characteristic of toxicity. If severe stomatitis develops, the drug should be discontinued temporarily.

The field of pediatric oncology offers many interesting areas for investigation, including the influence of genetic, maternal, and a variety of environmental factors upon a growing, dynamically changing host. In the future, one may anticipate important observations on the epidemiology of the important pediatric tumors which may lead to their prevention. Investigations into the etiology and the chemotherapy of cancer will undoubtedly provide more effective methods for treatment and management of the tumors of childhood.

REFERENCES

1. U. S. Bureau of Vital Statistics, 1947.
2. Cohen, L. S., and Thomison, J. B.: The Problem of Cancer in Children, Am. Practitioner **10**:1149, 1959.
3. Shimkin, M. B.: On the Etiology of Cancer, J. CHRON. DIS. **8**:38, 1958.
4. Furth, J.: A Meeting of the Ways in Cancer Research: Thoughts on the Evolution and Nature of Neoplasms, Cancer Res. **19**:241, 1959.
5. Cushing, H., and Wolbach, S. B.: The Transformation of a Malignant Paravertebral Sympatheticoblastoma Into a Benign Ganglioneuroma, Am. J. Path. **3**:203, 1927.
6. Gorrell, D. S.: Laryngeal Papillomata in Children, Canad. M.A.J. **67**:425, 1952.
7. Steward, J. K., Smith, J. L. S., and Arnold, E. L.: Spontaneous Regression of Retinoblastoma, Brit. J. Ophth. **40**:449, 1956.
8. Tivey, H.: The Natural History of Untreated Acute Leukemia, Ann. New York Acad. Sc. **60**:322, 1954.
9. Dargeon, H. W.: Cancer in Children From Birth to Fourteen Years of Age, J.A.M.A. **136**:459, 1948.
10. Farber, S.: Neuroblastoma, Am. J. Dis. Child. **60**:749, 1940.
11. Bodian, M.: Neuroblastoma, Pediat. Clin. North America **6**:449, 1959.
12. Everson, T. C., and Cole, W. H.: Spontaneous Regression of Cancer: Preliminary Report, Ann. Surg. **144**:366, 1956.
13. Steinbach, H. L., and Brown, R. F.: Retroperitoneal Tumors in Children: Roentgen Diagnosis, California Med. **78**:263, 1953.
14. Wittenborg, M. H.: Roentgen Therapy in Neuroblastoma—A Review of 73 Cases, Radiology **54**:679, 1950.
15. Sutow, W. W.: Prognosis in Neuroblastoma of Childhood, A.M.A. J. Dis. Child. **96**:299 1958.
16. Cresson, S. L., and Pilling, G. P.: Renal Tumors, Pediat Clin. North America **6**:473, 1959.
17. Silver, H. K.: Wilms' Tumor (Embryoma of Kidney), J. Pediat. **31**:643, 1947.
18. Abeshouse, B. S.: The Management of Wilms' Tumors as Determined by National Survey and Review of Literature, J. Urol. **77**:792, 1957.
19. Reese, A. B.: Tumors of the Eye. New York, 1951, Paul B. Hoeber, Inc.
20. Steward, J. K.: Malignant Disease, *in* Modern Trends in Pediatrics, London, 1958, Butterworth & Co., Ltd.
21. Reese, A. B., et al.: Treatment of Retinoblastoma by Radiation and Triethylenemelamine. A.M.A. Arch. Ophth. **53**:505, 1955.
22. Burnet, M.: Leukemia as a Problem in Preventive Medicine, New England J. Med. **259**:423, 1958.
23. Dameshek, W., and Gunz, F.: Leukemia, New York, 1958, Grune & Stratton, Inc.
24. Stewart, A.: Malignant Disease in Childhood and Diagnostic Irradiation in Utero, Lancet **2**:447, 1956.
25. Murphy, M. L.: Leukemia and Lymphoma in Children, Pediat. Clin. North America **6**:611, 1959.
26. Petrakis, N. L.: Bone Marrow Pressure in Leukemic and Non-Leukemic Patients, J. Clin. Invest. **33**:27, 1954.
27. Whiteside, J. H., Philips, F. S., Dargeon, H. W., and Burchenal, J.: Intrathecal Amethopterin in Neurological Manifestations of Leukemia, A.M.A. Arch. Int. Med. **101**:279, 1958.
28. Sullivan, M. P.: Intracranial Complications of Leukemia in Children, Pediatrics **20**:757, 1957.
29. Rhoads, C. P., editor: 6-Mercaptopurine, Ann. New York Acad. Sc. **60**:183, 1954.
30. Mustacchi, P., Stonfeld E. M., Lucia S. P., Petrakis, N. L.: Mortality in Acute Lymphocytic Leukemia, J. Nat. Cancer Inst. **23**:1397, 1959.

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DIAGNOSIS OF ANEMIA IN CHILDHOOD

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PLAN OF INVESTIGATION

INVESTIGATION of anemia is an orderly process requiring more diligence than inspiration: a careful history, physical examination, and certain laboratory determinations. The history may have to cover specifically diet, medication, exposure to toxins, a report of previous blood counts, the date anemia was first discovered, racial background, family history of anemia, jaundice, purpura, splenectomy, need for treatment with iron, liver extract, or transfusions. A complete physical examination is done with particular attention to color of skin and sclerae, presence of petechiae, bone pain, or tenderness.

The basic hematologic laboratory study of a patient with anemia includes: red cell count, hemoglobin, hematocrit; calculation of red blood cell indices; blood smear, reticulocyte, platelet, white cell counts; icterus index; bone marrow aspiration stained with Wright's stain for morphology and with the Prussian blue reaction for iron, and a urinalysis. Standard methods are used for these determinations.[1,2]

The red cell count is particularly valuable in characterizing the anemia since it is a measure of erythropoiesis and of red cell survival, but is not influenced by the rate of hemoglobin synthesis. When erythropoiesis is decreased, the red cell count is always low because there is no mechanism for compensatory prolongation of red cell life. On the other hand, with a moderate shortening of the red cell life span the red cell count may still be maintained at normal levels by a compensatory increase in erythropoiesis. A normal red cell count does, however, rule out those conditions which characteristically have very short red cell survival, for example, sickle cell anemia or conditions that depress erythropoiesis, such as infections. A normal red blood cell count with a low hemoglobin suggests iron deficiency as the cause of anemia, not infection. Red cell counting is unsuitable for routine laboratory use and should be considered a special procedure requiring

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TABLE I. IRON DEFICIENCY ANEMIA IN CHILDREN (12 PATIENTS IN EACH GROUP)

		RBC (MILLION/ MM.^{3})	HB. (GM./100 ML.)	HCT. (ML./100 ML.)	MCV (μ^3)	MCHC (%)	MCH ($\mu\mu$G)	RETIC. (%)
Hb. 4 Gm. % or less	Av.	2.7	3.1	14.2	54	22	12	2.5
	Range	1.7–3.5	2.3–3.6	9–17	43–62	18–26	9–14	0.1–4.2
Hb. 4-7.5 Gm. %	Av.	3.6	5.4	21	55	26	14	2.8
	Range	2.6–5.5	4.1–6.9	15–27	47–72	24–30	12–20	1.3–4.5
Hb. 7.5 Gm. % or more	Av.	5.1	8.8	32	65	27	17.5	1.4
	Range	4.4–6.3	7.6–10.4	22–39	48–89	23–29	12–23	0.7–2.0

great care—the counting of two pipettes and two chambers and a minimum of 1,000 cells. This reduces the intrinsic error and permits the accurate calculation of red blood cell indices.

The basic hematologic work-up outlined above establishes the diagnosis in most cases of anemia. Further tests are initiated only when this material has been evaluated properly.

We have found it convenient to ask ourselves four questions when approaching a person with anemia:

I. Is This Iron Deficiency Anemia?—The patient's history and clinical appearance, blood smear, red cell, and hemoglobin values frequently make the diagnosis obvious, but when the data are not sufficiently characteristic, the bone marrow stained for iron will give a definite answer. In iron deficiency anemia marrow hemosiderin is invariably lacking, while in all other anemias marrow hemosiderin is not only present but usually increased. If iron deficiency complicates some other form of anemia it is easier to treat the iron deficiency first and then re-evaluate the patient after hemoglobin values have become stablized at a higher level. Special care must be used in the evaluation of patients with

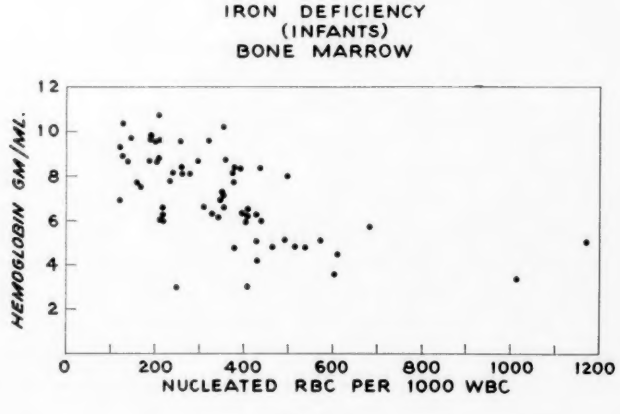

Fig. 1

hemolytic anemia where splenic activity is prominent, as, for example, in hereditary spherocytosis. In this type of disorder there may be relatively little iron in the marrow, but large amounts in the spleen.

II. Is This Megaloblastic Anemia?—The blood smear may show oval macrocytes, hypersegmented white cells, and pancytopenia, the marrow shows megaloblasts, giant metamyelocytes, and abnormal megakaryocytes. Failure to find these morphologic abnormalities when the red blood cell count is less than 2.5 million per cubic millimeter practically excludes the diagnosis of megaloblastic anemia, whether due to folic acid deficiency or vitamin B_{12} deficiency.

III. Is This Hemolytic Anemia?—There may be abnormal red cell morphology, reticulocytosis, leukocytosis, thrombocytosis, increased indirect bilirubin, and marrow erythroid hyperplasia; however, these changes may not be present. After iron deficiency and megaloblastic anemia have been ruled out by the bone marrow examination, and hemolytic anemia is suspected, one may wish to do a red cell survival study with Cr^{51} and perform some more specific tests, such as the Coombs test, Polyvynlpyrolidone, other agglutination tests, hemoglobin electrophoresis, determination of fetal hemoglobin, osmotic fragility, Schumm test for methemalbumin, and stain for Heinz bodies.[1,2]

IV. Is This Hypoactive Marrow?—Pancytopenia with few reticulocytes and with few cells on marrow aspiration suggests a marrow defect; this must be confirmed by a marrow biopsy, which may show increased amounts of fat, replacement by fibrous tissue, or infiltration by malignant cells. A bone survey by x-ray may reveal metastases.

In relative marrow failure erythropoiesis is normal but not increased; iron stores are adequate. Inadequate erythropoiesis may be associated with decreased liver, kidney, or thyroid function and appropriate tests are indicated.

SOME COMMON CAUSES OF ANEMIA

Iron Deficiency Anemia.—In iron deficiency anemia, symptoms are minimal and pallor noticed by the physician is the most frequent "presenting complaint," but there may be irritability, crankiness, and a history of poor diet. The skin is waxy-pale and transparent looking, and the sclerae slightly bluish without a trace of yellow. The hair may be brittle and lusterless; some children look fairly chubby but have very soft flesh. Occasionally, periorbital edema is seen and in perhaps 10 per cent of the cases the spleen is palpable. The blood count is frequently characteristic and immediately diagnostic (Table I). The red count stays relatively normal until the hemoglobin concentration becomes less than 7.5 Gm per 100 ml.; it is always relatively higher than the hemoglobin. This discrepancy is reflected (on the blood smear and in the red cell indices) by the marked hypochromia. The red cell count is usually above 2.5 million per cubic millimeter. One should at least question the diagnosis of iron deficiency anemia when the red count is below 2 million per cubic millimeter. The percentage of reticulocytes is often slightly elevated in severe iron deficiency anemia. A few strippled cells, target cells, and nucleated red cells may be seen. White cells and platelets have no characteristic pattern. In the bone marrow there is a rough correlation between the degree of anemia and the degree of erythroblastosis (see Fig. 1). The cells of

the entire red cell series are smaller than normal.[3] Normoblasts have very scanty cytoplasm and raggedy outlines. Bone marrow hemosiderin is invariably absent in such cases.

Mild iron deficiency anemia must be distinguished from thalassemia minor. Some of the hemoglobinopathies and infections may, at times, cause slight hypochromia but both red cell count and hemoglobin are decreased, even when there is relatively little anemia. In anemia without characteristic red cell indices, the presence or absence of bone marrow hemosiderin is of the greatest aid in eliminating or establishing the diagnosis of iron deficiency anemia.

We have found determination of the serum iron to be less useful than examination of the bone marrow for hemosiderin in the diagnosis of iron deficiency anemia. A low serum iron alone is not diagnostic; it may be seen not only in iron deficiency anemia but also in several medical illnesses including infections; only in conjunction with an increased total iron binding capacity does it have diagnostic value. These two determinations are more demanding of a technician's time, skill, and equipment, than the relatively simple diagnosis of iron deficiency anemia warrants.

Thalassemia Minor.—In this disorder symptoms are rare and diagnosis is often made only accidentally; there may be slight splenic enlargement. Thalassemia minor is the heterozygous form of thalassemia major; it is congenital, familial, found primarily in Italian, Greek, Spanish, and Chinese families, and does not change its course during life.

There is mild but persistent anemia with a hemoglobin rarely less than 9 Gm. but red cell count usually between 5 and 7 million (Table II). The red cells are very small and only moderately reduced in hemoglobin concentration (Fig. 2). Target cells and stippled cells may be present; there is considerable variation in size and shape of the red cells, more than in a patient with iron deficiency of a comparable degree of anemia. Reticulocytes may vary from 1 to 9 per cent; platelets and white cells are not remarkable. Fetal hemoglobin is not increased. A similar blood picture is found in one of the parents. The most helpful finding is the presence of hemosiderin in the bone marrow.

TABLE II. THALASSEMIA MINOR—12 PATIENTS

	RBC (MILLION/ MM.^{3})/	HB. (GM./100 ML.)	HCT. (ML./100 ML.)	MCV (μ^3)	MCHC (%)	MCH ($\mu\mu$G)	RETIC. (%)	MARROW IRON
Av.	5.5	10.4	34	64	30	19	2.6	2+
Range	4.7–7.0	8.3–12.0	23–40	51–78	27–33	17–23	1.5–4.7	1 − 4+

Thalassemia Major.—The homozygous form of this disease is a severe, lifelong, illness with chronic anemia, jaundice, and enlargement of the liver and spleen. The red count is low, Howell-Jolly bodies and nucleated red cells are numerous, fetal hemoglobin is increased. Life usually can be sustained only by regularly repeated transfusions.[4]

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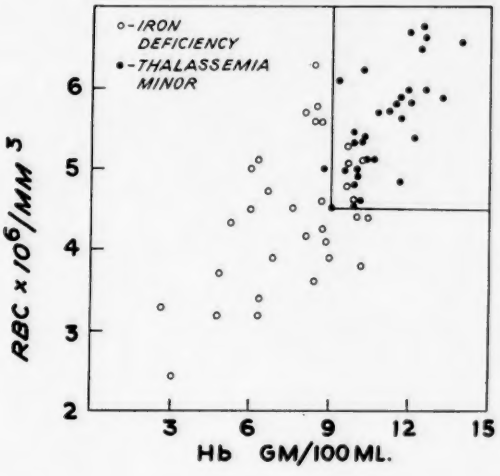

Fig. 2

Lead Poisoning.—In this disorder clinical findings are more prominent than the anemia. Abdominal colic, foot or wrist drop, and encephalopathy may simulate conditions calling for surgical intervention, poliomyelitis, and other infections of the central nervous system. The anemia is only moderately severe, usually hypochromic and microcytic; red cell stippling may be marked; the reticulocyte counts tend to be slightly higher than in iron deficiency anemia and the icterus index is slightly above normal rather than below normal as in iron deficiency anemia. Iron is present in the bone marrow. The presumptive diagnostic test is a urine coproporphyrin determination. Other tests may include determination of urine lead, particularly after treatment with EDTA (Table III).

TABLE III. LEAD POISONING (IN A PATIENT WITH THALASSEMIA-C DISEASE)

DAY	CA EDTA (MG./24 HR. I.V.)	RBC (MILLION/ MM.³)	NR/100 WBC	RETIC. (%)	WBC (THOUSAND /MM.³)	COPRO-PORPHYRIN (MG./24 HR.)	LEAD (MG./24 HR.)
0	0	3.7	134	6.1	28	390	255
1	1,200	3.9	137	7.5	21	1,060	665
2	1,200	——	——	——	——	914	8,700
3	1,200	——	——	——	——	1,210	8,400
4	0	——	——	——	——	750	5,250
5	1,200	4.1	54	10.2	——	950	1,230
6	0	——	——	8.4	——	675	4,050
7	0	——	——	5.6	——	1,370	1,000
8	0	4.1	14	5.9	8	623	580
9	0	——	——	7.5	7.2	——	——
10	1,200	——	——	3.5	——	——	——
11	1,200	——	——	4.0	——	350	6,650
12	1,200	——	——	2.2	——	8,450	5,000
13	0	4.7	5.5	6.0	9.8	8,500	5,000
14	0	——	——	2.2	——	——	——
15	0	——	——	2.7	——	1,420	390
20	0	5.6	0	1.4	23	——	——

TABLE IV. ANEMIA OF PREMATURITY—12 PATIENTS

	AGE (WEEKS)	RBC (MILLION /MM.^{3})	HB. (GM./100 ML.)	HCT. (ML./100 ML.)	MCV (μ^3)	MCHC (%)	MCH ($\mu\mu$G)	RETIC. (%)	MARROW IRON
Av.	6.5	2.8	8.7	28	90	33	31	5.5	2+
Range	5–8	2.3–3.5	7.2–10.8	25–32	75–100	31–35	23–39	2.1–9.7	0 – 4+

Anemia of Prematurity.—The anemia of prematurity, which occurs between the fifth and eighth weeks of life, gives rise to few symptoms or signs. The anemia is moderate; normocytic, normochromic reticulocytes and bone marrow erythroblasts may be increased in number (Table IV); marrow hemosiderin is still present. At 3 to 4 months the red blood count and hemoglobin values spontaneously return toward normal.[6]

Investigation for suspected hemolytic anemia in premature infants must take into account this normal fall and rise in blood values associated with reticulocytosis; diagnostic studies are best deferred until stable values are attained at approximately 4 months of age.

Hemoglobinopathies.—Negro patients with low red counts should be investigated for one of the hemoglobin anomalies. A proper study includes the sickle cell test (using sodium metabisulfite), hemoglobin electrophoresis, and determination of fetal hemoglobin on the patient and his parents.

The symptoms are most severe in sickle cell anemia. There is usually a history of recurrent attacks of pain in the arms, legs, and abdomen since childhood; however, the first clinical manifestations may be delayed for several years. There may be pallor of the mucous membranes and jaundice of the sclerae. Sickle cell and a few target cells are seen on the blood smear. The red count usually varies from 1.5 to 3.5 million per cubic millimeter; there may be a constant reticulocytosis of 15 to 20 per cent; there may be as many as 100 nucleated red cells per 100 white cells; leukocytosis of 20 to 40,000 is not unusual. In the bone marrow the myeloid to erythroid ratio is less than 1. Anemia, leukocytosis, and jaundice are relatively constant in these patients and do not change during crisis.

The other variants of sickle cell disease are less severe clinically, the spleen is usually enlarged and target cells are numerous. Heterozygous carriers, with few exceptions, are healthy from a clinical and hematologic point of view. The abnormal hemoglobins are discussed in detail in several recent reviews.[7,8]

TABLE V. HEREDITARY SPHEROCYTOSIS—6 PATIENTS

	RBC (MILLION/MM.^{3})	HB. (GM./100 ML.)	HCT. (ML./100 ML.)	MCV (μ^3)	MCHC (%)	MCH ($\mu\mu$G)	RETIC. (%)
Av.	3.7	10.2	27.6	75	37	26	6.6
Range	3.1–5.0	7.5–14.4	22–37	68–82	34–41	23–34	2.5–13.0

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Hereditary Spherocytosis.—This is a chronic, congenital, usually familial disorder of red cell formation characterized by spherocytosis and diminished resistance of red cells to hypotonic saline. When the disease presents in the newborn period with jundice and anemia, it must be distinguished from hemolytic disease of the newborn due to blood group incompatibility. The Coombs test, ABO typing of mother and child, and family hematologic study may be required in the differential diagnosis. More frequently, mild anemia, jaundice, and splenomegaly are first noticed in childhood. When hemoglobin levels are normal, the

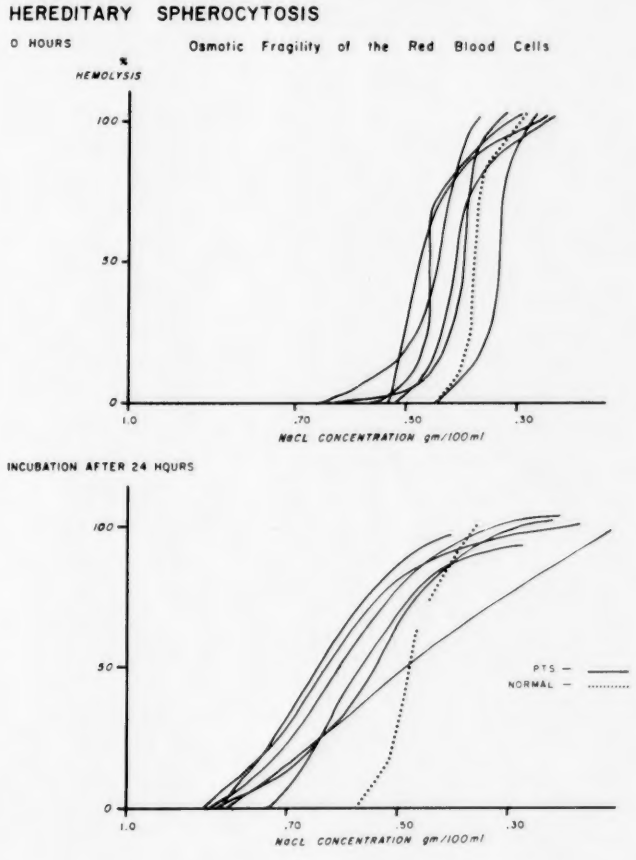

Fig. 3

disease may be recognized only because discovery of the disorder in some other member of the family leads to an intensive investigation of all relatives.

There may be family history of anemia, jaundice, or splenectomy; the patient's symptoms may include diminished energy and some retardation of growth. Anemia is mild or moderate, spherocytes are usually obvious on the blood smear. The red cell indices show a mean corpuscular volume just below normal and mean corpuscular hemoglobin concentration slightly above normal

—the only anemia with indices of this type (Table V). The reticulocytes are slightly elevated, indirect bilirubin may be up to about 2 mg. There is considerable erythroid hyperplasia of the bone marrow; marrow hemosiderin is present but not abundant. The osmotic fragility is increased but it may be necessary to incubate the blood for 24 hours at 37°C. to demonstrate the defect (Fig. 3).

Acute Hemolytic Anemia.—The presenting symptoms in this group of disorders usually are not those of anemia, but may suggest other clinical conditions. Chill, fever, nausea, vomiting, and abdominal pain simulate abdominal disorders requiring surgery. Weakness, drowsiness, dyspnea, tachycardia, and shock may cause suspicion of internal hemorrhage. The correct diagnosis frequently is made by the finding of a normochromic anemia with microspherocytes, distorted red

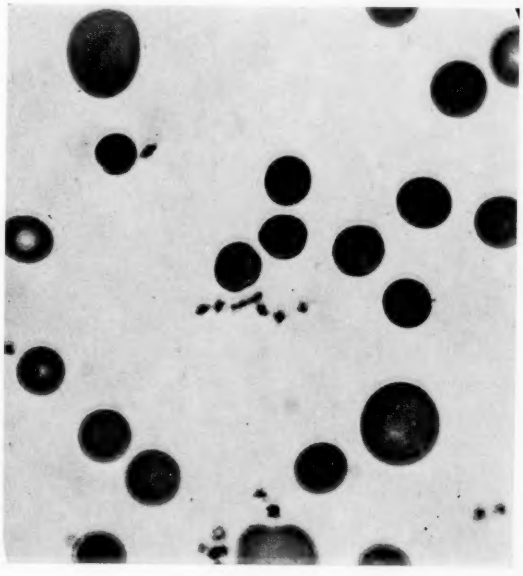

Fig. 4.—Acute hemolytic anemia. microspherocytes and poikilocytosis.

cells (Fig. 4), many reticulocytes, possible erythrophagocytosis (Fig. 5), and Heinz bodies (Fig. 6). The Coombs test is usually negative. Hemoglobinemia, methemalbuminemia (demonstrated by the Schumm test*) (Fig. 7), and elevated indirect bilirubin are especially helpful in distinguishing acute hemolytic anemia from blood loss. The hemolysis may be caused by certain medications such as sulfonamides or Phenacetin; it may be due to a combination of inherent red cell enzyme deficiency (glucose-6-phosphate dehydrogenase) plus a potential toxin such as napthalene (mothballs) or the fava bean; frequently, the mechanism and exact cause of the hemolysis remain obscure.[4,9]

*Shumm Test: Nine volumes of plasma are first covered with a layer of ether, and then one volume of a concentrated solution of ammonium sulfide is run in with a pipette and mixed. A positive reaction is indicated by the appearance of a hemochromogen with a sharply defined band at 558 μ.

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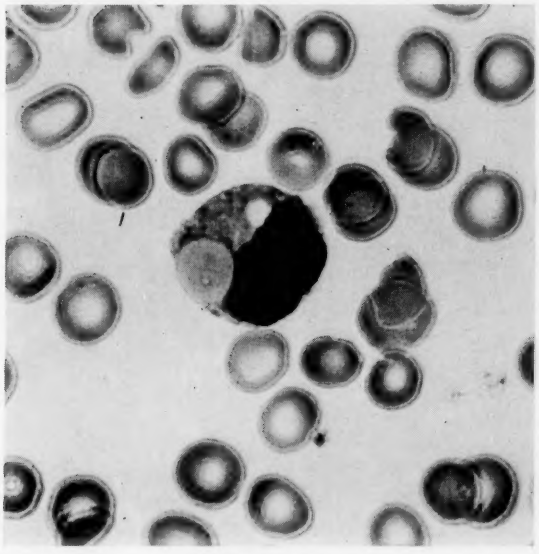

Fig. 5.—Acute hemolytic anemia. erythorophagocytosis.

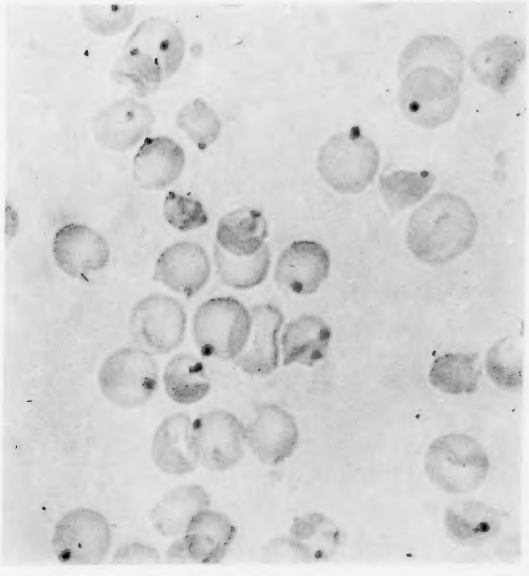

Fig. 6.—Acute hemolytic anemia. Heinz bodies. Heinz bodies stained with methyl blue appear as irregularly shaped bodies, eccentrically placed in the red cells close to the cell membrane. They may protrude from the erythrocytes by a stalk or occur free in the plasma. They are not visible on ordinary Wright's stain.

Idiopathic Acquired Hemolytic Anemia.—This term describes several disorders of different course and probably different etiology, having in common persistent autoantibodies.[4] Anemia varies from mild to severe; it may last a short time, then remit spontaneously, it may go on for years, or run an intermittent course. Jaundice and splenomegaly are almost invariably present, and occasionally there is an associated thrombocytopenic purpura. The anemia is macrocytic and normochromic with some variety in size and shape of red cells. Reticulocyte percentage is persistently elevated. There is a moderate increase in osmotic fragility. The number of white cells may be increased and erythrophagocytosis may be seen. The platelet count is normal or low. Marrow erythroid series is very active and hemosiderin is present. The Coombs test is always positive. The patient's own red cells and the red cells of normal donors have shortened survival in these instances.

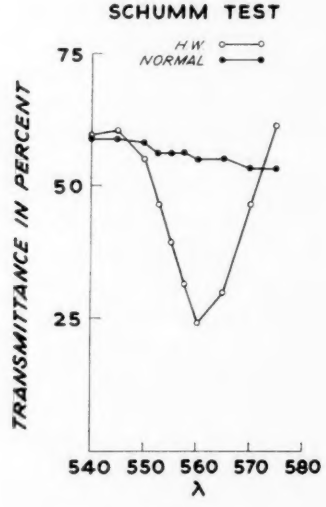

Fig. 7.—Acute hemolytic anemia.

Anemia of Infection.—Infections that cause anemia are usually clinically apparent and are of several weeks' duration. The anemia is not severe; the hemoglobin is rarely below 9 Gm. per 100 ml. and the red blood cell count is always below normal. The cells are normocytic and normochromic or slightly hypochromic; reticulocyte counts are normal. Bone marrow hemosiderin is present; serum iron is low as is the total iron-binding capacity.[10]

Some children with low-grade fever, an upper respiratory infection, decreased hemoglobin, which does not rise on oral therapy, are frequently misdiagnosed as having anemia of infection. Many of these children really are iron deficient and the correct diagnosis could have been made easily by finding a normal red blood cell count and absent marrow hemosiderin.

Congenital Hypoplastic Anemia.—Anemia is first noticed soon after birth; there may be progressive pallor, possibly weakness, but no jaundice, no enlarge-

ment of the liver, or the spleen. The reticulocyte count is well below 1 per cent, there are fewer than 40 nucleated red cells per 1,000 white blood cells in the marrow. The white cell and platelet population and bone marrow architecture are normal, and hemosiderin is present. There are no other clinical abnormalities. There is no response to vitamin B_{12}, folic acid, ascorbic acid, pyridoxine, or cobalt. Blood from normal donors survives normally in these patients. In perhaps half of the cases there may be a spontaneous remission.[11]

There are some drug-produced transient hypoplastic anemias, for example, following the use of chloramphenicol.[12] In the anemic phase of this condition, there is a severe reduction of reticulocytes and marrow nucleated red cells. Recovery is associated with reticulocytosis and erythroid hyperactivity of the bone marrow. While these changes are best documented for chloramphenicol, other medications and toxins may quite possibly produce similar pictures.

Congenital Nonspherocytic Hemolytic Anemia.—This term applies to a group of congenital hemolytic anemias which are not associated with altered red cell morphology, osmotic fragility of the red cells, or an abnormal hemoglobin electrophoresis. The diagnosis is made by exclusion of other well-recognized hemolytic disorders. Isotope studies show a greatly reduced red cell life span and intense erythropoiesis, with little sequestration of red cells in the spleen.[13] The etiology is probably diverse as is suggested by variations among different patients in the amount of autohemolysis, the degree of increased osmotic fragility on incubation of the red cells in vitro, the nature of cation changes, the utilization of glucose, the stability of glutathione, and the concentrations of adenosine triphosphate and glucose-6-phosphate dehydrogenase in the red cells.[14] The exact nature of the genetically determined biochemical abnormalities is unknown. The disease is usually transmitted as a Mendelian dominant. The following case illustrates some of these features.

R. B., a 5-year-old white girl of Irish-Norwegian descent, was first discovered to be anemic on routine preschool examination. She had grown and developed normally, but had always been pale, had had frequent upper respiratory infections, and was somewhat awkward in her movements. Recently she had noted poor appetite, some dyspnea on exertion, and severe nocturnal leg cramps. The patient's parents and 4-year-old sister were well and not anemic.

The pertinent findings on physical examination were as follows: The patient was an alert, pallid, white girl, 46 inches tall. Her weight was 45½ pounds, pulse 90, blood pressure 110/70 mm. Hg, temperature 37.4°C. with slight frontal bossing. No purpura or lymphadenopathy was evident. The heart and lungs were clear. The spleen was palpable four fingerbreadths below the left costal margin. The liver was palpable one fingerbreadth below the right costal margin. The extremities and neurogical examination were normal.

Laboratory examinations showed: red blood count 3.6 million/mm.^{3}; hemoglobin 9.7 Gm./100 ml.; hematocrit 33 ml./100 ml.; mean corpuscular volume 92 μ^3; mean corpuscular hemoglobin concentration 29 per cent; mean corpuscular hemoglobin 27 $\mu\mu$g; reticulocytes 15.3 per cent; nucleated red blood cells 0.5/100 white blood cells. There were some microcytic and some stippled red cells. Platelets and white cells were normal in number and appearance.

The bone marrow showed marked hyperplasia of the red cell series with clusters of normoblasts and a myeloid to erythroid ratio of 1 to 3. The megakaryocytes and white cells were not remarkable; the hemosiderin was ample. The direct bilirubin was 0.3 mg./100 ml., indirect 2.6 mg./100 ml.; hemoglobin electrophoresis, serum proteins, uric acid, creatinine normal; Coombs test negative.

A quantitative direct erythrocyte osmotic fragility test showed increased resistance, but on incubation at 37°C. for 24 hours a small proportion of the cells became more fragile than normal.

Red cell volume (P^{32}) was 16 ml./kg. (normal 24-33 ml./kg.); plasma volume 53.8 ml./kg. (normal 32-45 ml./kg.); total blood volume 69.8 ml./kg.; plasma iron 205 μg/100 ml. (normal 70 to 170 μg/100 ml.); total plasma iron-binding capacity 257 μg/100 ml. (normal 300 to 425 μg/100 ml.); plasma iron turnover 1.7 mg./hr./liter of blood (normal 0.22 to 0.38 mg./hr./liter). Radioiron appeared in circulating erythrocytes more rapidly than normal, but attained a maximum net incorporation of only 46.5 per cent (normal 85 to 100 per cent). Analysis of plasma radioiron for a period of 11 days showed a daily formation of 17.7 Gm. of hemoglobin or 11.5 Gm. of hemoglobin/day/liter of blood (normal 1.0 to 1.6 Gm./day/liter of blood). When related to total body hemoglobin of 133 Gm. this resulted in a mean erythron life span of 7.5 days (normal 102 to 132 days).

In vivo measurements show rapid accumulation of radioiron in the sacral marrow, being complete at 3 hours. There was no initial accumulation of radioiron in either the liver or spleen. During the next 11 days there was a secondary release of radioiron from the sacral marrow accompanied by moderate secondary accumulation of radioiron in the liver.*

This iron kinetic study was interpreted to show marked shortening of erythrocyte life span, accompanied by partially compensatory marked increase of erythropoiesis. Though some red cells were sequestered and destroyed in the spleen most of the erythrocytes were removed from the circulation and destroyed elsewhere.

Miscellaneous Conditions.—Moderate to severe anemia is frequently associated with a variety of clinical conditions diagnosed rather easily by their marrow or lymph node abnormality, for example, leukemia, lymphosarcoma, neuroblastoma. Sometimes anemia is secondary to some striking clinical disorder, such as Caffey-Smyth disease, ectodermal dysplasia, osteopetrosis, or myxedema.

Some forms of anemia have no underlying hematologic or systemic disease, do not fit clearly into the hemolytic or aplastic categories, and resist all forms of therapy. These anemias are best categorized by isotope studies that measure red cell life span, marrow activity, and effective erythropoiesis.[15] The following case of refractory normoblastic anemia[16] serves as an example.

R. B., a 12-year-old boy of Italian decent, was first discovered to be slightly anemic at 9 years of age. Growth and development were normal. The child had always felt well and had suffered no serious illnesses. He had become jaundiced a few hours after birth but this cleared quickly. The first blood count at 4 years of age, at the time of a tonsillectomy, had shown a hemoglobin concentration of 13.0 Gm. per 100 ml. A repeat count at age 9 showed red blood count 3.75 million per cubic millimeter; hemoglobin 9.9 Gm. per 100 ml.; white blood count 5,800 per cubic millimeter, differential count normal. Repeat counts since that time had shown similar values, and although the child was asymptomatic, the parents requested further investigation of the anemia. The mother, father, and two brothers aged 9 and 11 were living and well and had no anemia.

Pertinent findings in physical examination were as follows: the patient was an alert well-developed boy; weight 112 pounds; pulse 72; blood pressure 112/60 mm. Hg. There was minimum pallor of the skin and no icterus, purpura, or lymphadenopathy. The heart and lungs were clear. The tip of the spleen was palpable on deep inspiration. The extremities, genitals, and neurological examination were normal.

Laboratory examinations showed: red blood count 3.4 million/mm.^{3}, hemoglobin 11.2 Gm./100 ml., hematocrit 35 ml./100 ml., mean corpuscular volume 107 μ^3, mean corpuscular hemoglobin concentration 31 per cent, mean corpuscular hemoglobin 33 $\mu\mu$g. Except for slight macrocytosis the blood smear appeared normal. The white cells and platelets were normal in number and

*Ferrokinetics measurement were done by Dr. Myron Pollycove at the Donner Laboratory of the University of California.

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appearance. Serum bilirubin direct was 0.19 mg. per cent, indirect 1.35 mg. per cent. The direct and 24 hour incubated osmotic fragility tests were normal. The glucose-6-phosphate dehydrogenase screening test was normal. The hemoglobin electrophoresis was normal and there was no increase in fetal hemoglobin.

The bone marrow showed marked erythroid hyperplasia without apparent asynchrony of nuclear and cytoplasmic development. The myeloid to erythroid ratio was 1 to 3. Megakaryocytes were present in normal numbers, hemosiderin ample. The white blood cell series was active although overshadowed by the erythroid hyperplasia. Of particular interest was the presence of considerable erythrophagocytosis.

The half-life of the red cells determined by the radioactive chromic phosphate method was 30 days (normal 28 to 35 days). The spleen-liver count ratio at 7 days was 1.4 to 1 and at 14 days was 1.1 to 1.

Total proteins, serum electrophoresis, Bromsulphalein concentration, and serum creatinine, were normal. Cold agglutinins, isoagglutinins and the Coombs test were negative; fecal urobilinogen 190.0 mg./24 hours; urine urobilinogen 6.32 mg./24 hours. Plasma iron 109 μg/100 ml.; total iron binding capacity of plasma 383 μg/100 ml.; plasma iron turnover 0.85 mg./hr./liter of blood.

Net incorporation of radioiron into circulating erythrocytes was delayed, attaining a maximum in 2 weeks of 43 per cent (normal 85 to 100 per cent). Analysis of plasma radioiron for 2 weeks showed daily synthesis of 19.8 Gm. hemoglobin, 5.5 Gm./day/liter of blood (normal 1.0 to 1.6 Gm./day/liter of blood). When related to total body hemoglobin of 436 Gm., which remained constant during the period of study, a mean erythron life span of 22 days was obtained (normal 100-135 days).

In vivo measurements showed rapid initial accumulation of radioiron in the sacral marrow without significant accumulation in either the liver or the spleen. Subsequently, there was gradual, incomplete net release of radioiron from the sacral marrow accompanied by slow progressive secondary accumulation of radioiron in the liver and slight secondary accumulation of radioiron in the spleen.*

This iron kinetic study was interpreted to show considerable shortening or erythron life span associated with moderate destruction of red cells in the marrow. This functional defect is of the same type as those seen in pernicious anemia but much less severe. The iron kinetic pattern is characteristic of anemia with prominent intramedullary hemolysis.

REFERENCES

1. Ham, H.: A syllabus of Laboratory Examinations in Clinical Diagnosis, Cambridge, Mass., 1950, Harvard University Press.
2. Cartwright, G.: Diagnostic Laboratory Hematology, ed. 2, New York, 1958, Grune & Stratton, Inc.
3. Wallerstein, R. O.: Unpublished data.
4. Dacie, J. V.: The Hemolytic Anemias, New York, 1954, Grune & Stratton, Inc.
5. Watson, R. J., Decker, E., and Lichtman, H. C.: Hematologic Studies of Children With Lead Poisoning, J. Pediat. **21**:40, 1958.
6. Schulman, I., Smith, C. H., and Stern, G. S.: Studies on the Anemia of Prematurity, A.M.A. Am. J. Dis. Child. **88**:567, 1954.
7. Chernoff, A. I.: The Human Hemoglobins in Health and Disease, New England J. Med. **253**:322, 365, 416, 1955.
8. Singer, K.: Hereditary Hemolytic Disorders Associated With Abnormal Hemoglobins, Am. J. Med. **18**:633, 1955.
9. Beutler, E.: The Hematologic Effect of Primaquine and Related Products. A Review, Blood **14**:103, 1959.
10. Cartwright, G. E., and Wintrobe, M. M.: The Anemia of Infection. A Review, Advances Int. Med. **5**:165, 1952.
11. Smith, C. H.: Hypoplastic and Aplastic Anemias of Infancy and Childhood, J. Pediat. **43**:457, 1953.
12. Saidi, P., and Wallerstein, R. O.: Effect of Chloramphenicol on Erythropoiesis, Clin. Res. **8**:131, 1960.

*Ferrokinetics measurement were done by Dr. Myron Pollycove at the Donner Laboratory of the University of California.

13. Motulsky, A. G., Crosby, W. H., and Rappaport, H.: Hereditary Nonspherocytic Hemolytic Disease, Blood **9**:749, 1954.
14. Zinkham, W. H., and Lenhard, R. E.: Metabolic Abnormalities of Erythrocytes From Patients With Congenital Nonspherocytic Anemia, J. Pediat. **55**:319, 1959.
15. Pollycove, M.: Iron Kinetics, in Wallerstein, R. O., and Mettier, S. R., editors: Iron in Clinical Medicine, Berkeley, Calif. 1958, University of California Press, pp. 43-57.
16. Dacie, J. V., Smith, M.D., White, J. C., and Mollin, L. D.: Refractory Normoblastic Anemia: A Clinical and Hematologic Study of Seven Cases, Brit. J. Haemat. **5**:56, 1959.

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METABOLIC DISEASES OF CHILDHOOD

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RECENT advances in knowledge in biochemistry and in genetics have altered the concepts and stimulated a great interest in the "inborn errors of metabolism."

An exact delineation of the metabolic diseases of childhood is difficult because some of the less common and poorly understood disorders which have been historically classified as "metabolic" are now grouped in other categories. At the same time the use of "metabolic" in its broadest sense would add many diseases that, until recently, were grouped according to the organ or system most affected. Because the manifestation of these latter diseases is localized, they may still be best classified with other diseases of that system, even though the basic defect is an inability to synthesize a normal amount of a given substance. It is easier, for example, to think of sickle cell anemia as a disorder of the hematopoietic system and to group it with other anemias than to recognize its relationship to congenital adrenal hyperplasia. In the purest sense, however, perhaps all hereditary conditions could be called "metabolic," and many other diseases included also which are not presently thought to be genetically determined.[1]

In the past, failure to recognize the familial incidence in some cases was due not only to a lack of understanding of the more complicated modes of inheritance but also to the environmental modifications in manifestations of a given disorder. Zollner,[2] in a recent review in this JOURNAL, emphasized the role of the external factors superimposed on the genetic background. An individual with an inherent deficiency in a specific metabolic pathway which is never tested during his life would obviously not be recognized as having such a deficiency. The length of time of the "testing" is important also. A disorder which seems to appear later in life and is thought to be dominant in inheritance actually may be the result of the inability of a heterozygote to withstand metabolic stress for a long period of time.

Infants and children, if not quantitatively "a different species" from the adult in bodily reactions, at least vary tremendously in body physiology and in chemical pathways of metabolism. These differences are seen usually in the most exaggerated form in the premature infant. This difference in function causes some

conditions which are also metabolic in nature (defective tyrosine metabolism in the premature[3]) but are temporary and disappear with time and maturity. One might expect then that all the metabolic disorders would lessen in intensity as the growing individual acquires biochemical maturity. While this does occur, in general the early appearance of a metabolic disease indicates a process of severity which may require lifelong treatment. Clinically, however, the temporary inadequacies also are of great importance to the pediatrician. An example is the recent interest in the limitation of glucuronide conjugation in infancy which results not only in a failure to metabolize substances such as bilirubin and steroid compounds at the same rate as does the adult, but also in an inability to detoxify certain drugs to a degree that these medications become dangerious to use in infants.[4]

Currently, the inherited disorders are thought to be due to an inability to produce a normally structured protein in the amounts normally found in the body. There may be complete absence or decreased synthesis of a protein which itself serves a vital function (congenital agammaglobulinemia, hemophilia, etc.). There may be the formation of a protein that differs only very slightly in molecular configuration from that of the normal but with sufficient malformation to cause disease manifestations (sickle cell anemia and other hemoglobinopathies). Finally there may be an absence or deficiency of a protein which is necessary as an enzyme for a chemical reaction and which occurs either primarily in a single organ or in the body as a whole. This enzymatic block may then cause disturbance by a lack of an essential end product of the reaction (goitrous cretinism), or by the effect of precursors which have been accumulated by the interference with the reaction (phenylketonuria). Detection of the disorder may depend upon demonstration in blood or urine of a diminished amount of the end product of the reaction, or of an abnormal amount of a precursor, or of products from an alternate metabolic pathway.

This discussion will be concerned with some of the diseases in childhood which are caused by lack of enzymes and which have generalized manifestations. Ideal treatment would be to supply the enzyme which is deficient or inactive. At present this is not possible and current therapy depends upon the supply of an essential substance or the avoidance of accumulation of toxic precursors.

PHENYLPYRUVIC OLIGOPHRENIA (PHENYLKETONURIA)

Phenylpyruvic oligophrenia, also called phenylketonuria, is an inherited enzymatic defect causing mental retardation usually of a severe degree. Recently, it has been demonstrated that avoidance of accumulation of precursors can ameliorate the disease manifestations. Great emphasis is placed on early detection, as this is one of the few types of mental retardation that appears to be preventable.

The basic defect in phenylketonuria is the lack of an adequate amount of the enzyme (phenylalanine hydroxylase) which converts phenylalanine to tyrosine. This results in a great increase in the levels of phenylalanine in the serum and urine and of its conversion products: phenylpyruvate, phenylacetate, and phenyllactate. The detection in the urine of phenylpyruvate in the form of

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phenylpyruvic acid, by its reaction with ferric chloride, gave this disease its original name. Experimental evidence indicates that these patients have a reduction in tyrosine products and, clinically, this is evidenced by decreased melanin and epinephrine synthesis.[5]

Patients with phenylketonuria have an intelligence quotient that is most frequently in the 0 to 25 category and only very rarely does intelligence approach the borderline normal levels. Early gross motor development may be close to normal,[6] so that the degree of retardation may not be recognized in infancy. These children are frequently irritable and difficult to manage although occasionally they may be stuperous. Various non specific neurological abnormalities are common. Seizures occur in about 25 per cent and electroencephalograms are abnormal in about 75 per cent of the patients.[6]

The typical child with phenylketonuria is fair skinned, fairhaired, and blue eyed. While this is not always so, the degree of pigmentation is usually less than would be anticipated by genetic background. Skin inflammations are common, the most frequent being eczema.

Studies still in progress indicate that if this disease is detected in infancy and phenylalanine intake is limited, the infant is capable of normal development provided that dietary control is instituted early enough. This would confirm the theory that the retardation results from toxic effect of phenylalanine or related substances on cerebral development rather than from a separate cerebral abnormality. Older patients on the elimination diet show improvement in dermatological and neurological sequelae, and may be easier to manage from the standpoint of behavior, but no significant relief in the mental retardation has been noted. The penylalanine-free diet is now commercially available* but nutritional disorders, not yet completely understood, anemias, and skin rashes have been reported during its use. Judicious clinical care must be exercised in estimating the amount of phenylalanine that should be added to prevent these complications. Since the diet is expensive, and requires careful medical supervision, its use is not advised for the older patient, who will gain only partial improvement.[7]

The worth of the diet, if instituted soon after birth, has been established and a more intense effort toward early detection is warranted. In a family which has produced a child with phenylketonuria, any subsequent child should be checked as soon after birth as possible. While the urine test may not become positive for a period of weeks, the serum phenylalanine levels become elevated within a matter of hours. In order to discover cases where no familial incidence is known, many pediatricians and clinics have begun to do routine testing of urine during well-baby visits. Besides the ferric chloride test, several new procedures are available.[8]

GLYCOGEN STORAGE DISEASE OF THE LIVER (VON GIERKE'S)

Deficiencies of at least three distinct enzymes cause an abnormal accumulation of glycogen in the liver and, to a lesser extent, in the kidneys and skeletal muscles. The most common type is an absence or a deficiency of the enzyme (glucose-6-phosphatase) which converts glucose-6-phosphate to free glucose.

*Lofenalac, Mead Johnson & Company.

Less common are the conditions in which the enzymes necessary for normal branching and debranching of glycogen are absent, resulting in storage of an abnormally configured glycogen. Other enzymatic deficiencies also probably occur, since a few of the reported cases do not clearly fit into any of these three types. These (four or more) types of hepatic glycogen storage do not appear to be related to glycogen storage disease of the heart (Pompe's syndrome).[9]

Classic von Gierke's disease is characterized by an enlarged liver, slowness of growth—with height more affected than weight, frequent infections, a tendency to acidosis, and, rarely, hypoglycemic manifestations. Laboratory studies reveal a low fasting blood sugar, a high and prolonged glucose tolerance curve, and little elevation of the blood sugar in response to epinephrine and glucagon administration. Diagnosis depends upon the demonstration, microscopically and chemically, of increased glycogen in the liver and either a low glucose-6-phosphatase activity or an abnormal configuration of the glycogen in the liver.

In treatment, frequent feedings of a high protein diet are used in an attempt to supply a more uniform level of blood glucose and to prevent excess glycogen deposition. Infections and acidosis should be treated early and rigorously. This treatment does not affect the basic disorder and some patients die in infancy, though the severity seems to be variable and an occasional case may be mild.[10] There is some evidence that if the child survives infancy the disease manifestations lessen.[11]

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GALACTOSEMIA

Galactosemia is a rare recessive deficiency of the enzyme (p-gal-uridyl-transferase) which converts galactose-1-phosphate to glucose-1-phosphate. Galactose is produced by a breakdown of lactose in the intestine, and failure to metabolize this substance further leads to accumulation in the blood and excretion in the urine where it is detectable as a reducing substance. The elevated blood galactose causes cataracts and hepatic and renal damage. Hepatomegaly, jaundice, feeding difficulties, and malnutrition are common findings. Liver function tests reflect some degree of damage and cirrhosis may develop. Mental retardation also occurs; it is not certain whether this is a direct toxic effect of the galactose or a consequence of hypoglycemia. (The reducing substance in the serum may be normal but the true glucose level is lowered.) The triad of hepatomegaly, cataracts, and mental retardation should cause one to suspect this disease. Laboratory studies should include identification of the reducing substance as galactose, careful evaluation of the blood galactose, and galactose tolerance test. These studies may vary considerably in the normal infant, particularly when recovering from diarrhea.[12]

Treatment of galactosemia consists of limiting dietary lactose. A nonmilk formula must be used and milk products avoided. The disease manifestations are reversible to some extent, but early detection should be emphasized since the mental retardation can be avoided only if treatment is instituted before irreparable damage has occurred. Galactosemic children can tolerate small amounts of milk products later in childhood, and there is some laboratory evidence to indicate the development of an alternate metabolic pathway to tolerate limited amounts of galactose.[13]

CYSTINURIA

Cystinuria is a not uncommon disorder in the reabsorption by the renal tubules of cystine, lysine, arginine, and ornithine which results in increased urinary excretion of these four amino acids. The exact mechanism of the abnormality is unknown. The serum concentrations of these substances are not altered, and there are no generalized manifestations, although some persons with cystinuria form renal stones readily. Anyone with a strong family history of renal stones or any child who develops renal stones should be investigated for cystinuria. Reduction of stone formation can be accomplished by increased fluid intake and alkalinization, although an occasional patient needs further treatment. The use of a diet restricted in methionine (a cystine precursor) and possibly other precursors has been suggested.[14]

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CYSTINOSIS (CYSTINE STORAGE DISEASE)

Cystinosis is a much less common and more severe condition associated with dwarfing, renal rickets, acidosis, sometimes hypokalemia, and, ultimately, renal failure and death. The names of Fanconi, Lignac, Debré, and de Toni have been associated with reports of this or similar disorders. In cystinosis the aminoaciduria is generalized, and it is accompanied to a varying degree by other renal tubular abnormalities: glycosuria, phosphaturia, lack of response to antidiuretic hormone (nephrogenic diabetes insipidus), and loss of fixed base—particularly potassium. Cystine crystals are deposited through the body and can be demonstrated clinically in the corneas and the bone marrow.

Cystinosis combines features which are usually seen as single disease entities. Although most authorities classify it as a renal tubular defect, there is not general agreement; this classification does not explain why generalized deposition of cystine occurs.[15] The treatment, at present, is entirely symptomatic and directed to the particular stage of the disease which is manifest.

MAPLE SUGAR URINE DISEASE

Recently, a severe, progressive, neurological disorder associated with the excretion of urine which has an odor like that of maple sugar has been described.[16,17] The incidence is familial, the onset is early in infancy, and the outcome is fatal. The metabolic abnormality is in the degradation, probably at the oxidative decarboxylation level, of the branched chain amino acids; and increased amounts of valine, leucine, and isoleucine are found in the blood and urine. Although studies of the disease are sparse, attempts at dietary control are being tried.[17]

PENTOSURIA AND FRUCTOSURIA

Familial errors in the metabolism of the five-carbon sugar pentose or xylulose and the six-carbon sugar fructose are rare and of no apparent consequence. Both of these sugars reduce Benedict's solution, and the only clinical importance in pentosuria and fructosuria is to distinguish them from diabetes mellitus.

REFERENCES

1. Hsia, David Y.-Y.: Inborn Errors of Metabolism, Chicago, 1959, The Year Book Publishers, Inc.
2. Zöllner, Nepomuk: Inborn Disorders of Metabolism, J. CHRON. DIS. **10**:6, 1959.
3. Levine, S. Z.: Tyrosine and Phenylalanine Metabolism in Infants and the Role of Vitamin C[1], Harvey Lectures, ser. 42, Lancaster, Pa., 1947, Science Press, pp. 303-333.
4. Kretchmer, N.: Practical Therapeutic Implications of Immaturity, Pediatrics **23**:638, 1959.
5. Kretchmer, N., and Etzwiler, D. D.: Disorders Associated With the Metabolism of Phenylalanine and Tyrosine, Pediatrics **21**:445, 1958.
6. Paine, Richmond S.: The Variability in Manifestations of Untreated Patients With Phenylketonuria (Phenylpyruvic Aciduria), Pediatrics **20**:290, 1957.
7. Hsia, David Y.-Y., Knox, W. E., Quinn, K. V., and Paine, R. S.: A One-year, Controlled Study of the Effect of Low-Phenylalanine Diet on Phenylketonuria, Pediatrics **21**:178, 1958.
8. Baird, H. W., III: A Reliable Paper-Strip Method for the Detection of Phenylketonuria, J. Pediat. **52**:715, 1958.
9. di Sant'Agnese, P. A., Andersen, D. H., and Mason, H. H.: Glycogen Storage Disease of the Heart. II. Critical Review of the Literature, Pediatrics **6**:607, 1950.
10. Zetterström, R., and Sörbo, Bo: Glycogen Storage Disease of the Liver. Report of an Atypical Case With Studies of the Glycogen Structure and the Glucose-6-phosphatase Activity of the Liver, Acta paediat. **45**:269, 1956.
11. Cori, G. T., and Cori, C. F.: Glucose-6-phosphatase of the Liver in Glycogen Storage Disease, J. Biol. Chem. **199**:661, 1952.
12. Hartmann, A. F., Grunwaldt, E., and James, D. H., Jr.: Blood Galactose in Infants and Children, J. Pediat. **43**:1 1953.
13. Isselbacher, K. J.: Evidence for an Accessory Pathway of Galactose Metabolism in Man, J. Clin. Invest. **36**:902, 1957.
14. Smith, D. R., Kolb, F. O., and Harper, H. A.: The Management of Cystinuria and Cystine-Stone Diseases, J. Urol. **81**:61, 1959.
15. Piel, Carolyn F.: Diseases of the Renal Tubules in Childhood, Pediatrics **20**:337, 1957.
16. Menkes, J. H., Hurst, P. K., and Craig, J. M.: A New Syndrome: Progressive Familial Infantile Cerebral Dysfunction Associated With an Unusual Urinary Substance, Pediatrics **14**:462, 1954.
17. Dancis, J., Levitz, M., and Westall, R. G.: Maple Syrup Urine Disease: Branched Chain Keto-aciduria, Pediatrics **25**:72, 1960.

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CLINICAL EVALUATION OF HEART DISEASE IN CHILDREN

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IN THE past few years there has been a great change in the approach to the diagnosis and management of heart disease in children, due chiefly to the stimulation of advances in surgical corrective techniques, and made possible by intensive application of physiologic and radiologic methods to the study of heart function. Correlation of data obtained by cardiac catheterization and angiographic studies with physical signs, electrocardiography, and roentgen examination has made for more reliable clinical assessment. It is possible, however, for the clinician without complicated or specialized techniques to make a very useful evaluation of the structural and physiologic status of the heart on which opinions can be based in regard to clinical management, allotment of activity, vocational counselling, indications for surgery, or need for more detailed studies. "Clinical evaluation" for this purpose includes history, physical examination, electrocardiogram, red blood cell count with hemoglobin and hematocrit determinations, and an x-ray study of the chest. Frequently, it is possible to predict from the physical signs what the electrocardiogram and the chest x-ray study will show.

In evaluating the significance of a heart murmur, one is interested primarily in judging the functional efficiency of the heart and whether it is performing its function without undue effort or strain. Regardless of the etiology or the intensity of the murmur, clinical recommendations should be based on evidence of cardiac competence and efficiency.

Initial assessment of a child with a heart murmur consists of evaluation of the history and the general physical state. Clinical histories may be misleading, being modified by apprehension and overprotection. A parent who knows of the presence of a murmur in a child will tend to observe more closely and will frequently overinterpret clinical signs such as variation in respiratory pattern, blueness, pallor, cardiac activity, and even body size.

Presence or absence of cyanosis is frequently unreliable from the history. Parents, and even nurses and physicians, will tend to overinterpret normal infantile circulation and vasomotor changes, (acrocyanosis, flushing, pallor) as cyanosis. On the other hand, even rather marked cyanosis may be overlooked,

particularly in persons with olive or dark skins or in persons with anemia. The time that cyanosis is first observed by parents coincides frequently with the time at which a heart murmur was commented upon by the physician. Cyanosis in the infant may be from many causes other than right-to-left shunts.

Growth retardation is not well evaluated unless it is related to other members of the family. Children are frequently described as "very thin" or "small," this being assumed to be a manifestation of heart disease. A look at other members of the family may make the family variant obvious and, in the family group, the child may fall into a perfectly normal pattern.

The most common problem in cardiac evaluation in children is that presented by the otherwise normal child who is found to have a heart murmur. The exact cause of the murmur is less important than ascertaining whether there is any associated impairment of circulatory function or any increased work load on the heart, whether it represents a condition which may lead to complications, and what the prognosis may be in terms of activity and longevity for the child.

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The term "functional" or "benign" is used to refer to the murmur with which there is no evidence of increased cardiac work load or circulatory disturbance and with which the heart's response to exercise stress is normal. The typical venous hum and the functional murmur may be stated with confidence to be associated with no significant anatomic abnormality; the "benign" murmur of childhood may also include those murmurs associated with minor anatomic variants such as small septal defects with small shunts or mild valvular lesions which may give rise to turbulence but do not impose significant obstruction or valvular incompetence. Idiopathic dilatation of the pulmonary artery may cause a soft palpable thrill with a soft systolic murmur in the second left intercostal space at the left sternal edge and the x-ray finding of a prominent main pulmonary artery segment, with physical signs of a heart that is not enlarged nor hyperactive and an electrocardiogram with no evidence of an increased right ventricular work load.

The so-called "functional murmur" is a high-pitched murmur, often described as "musical" or "vibrant," of Grade 1 to 2 intensity, best heard usually in the left third intercostal space, not widely transmitted, associated with heart sounds of normal quality and intensity in all areas, not associated with cardiac enlargement or hyperactivity, thrills, heaves, or abnormality as seen on the electrocardiogram or the x-ray; the blood pressure is normal; the response of the heart to exercise is normal. This type of murmur is heard most commonly during the middle childhood years, and may be heard only on one or two examinations, or may persist for several months or years. It is sometimes heard in association with a prominent venous hum. This type of murmur may be much louder and harsher under conditions of increased cardiac output with apprehension, exertion, fever, or with anemia. When such a murmur is heard in a febrile or excited child whose heart rate is rapid, one may not be confident of the innocent nature of the murmur until the child is re-examined under more normal circumstances. Murmurs heard in children with marked anemia may simulate those of patent ductus, septal

defects, and valvular incompetence and are associated with cardiac enlargement and hyperactivity. Such hearts cannot be evaluated adequately for underlying heart disease until the anemia is corrected.

The venous hum may be so loud and vibrant that it is mistaken for evidence of an arteriovenous fistula of the neck. It is heard as a variable or continuous sound, maximal at the right upper sternal border or just above the head of the right clavicle, and sometimes associated with a palpable thrill just above the clavicular head. It differs from a fistula in that the diastolic portion of the murmur is easily obliterated and the systolic component is markedly altered by changes in position of the head, by postural changes such as reclining, and by light pressure exerted over the jugular vein. It is not associated with hyperactivity of the heart, tachycardia, wide pulse pressure, cardiomegaly, or electrocardiographic abnormalities. Like the functional precordial murmur, it may be heard only on one or two examinations, or it may persist for several years.

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The term "benign cardiac murmur of childhood" or "innocent" murmur may be applied to murmurs other than those described, which occur in conjunction with thrills, minor electrocardiographic or x-ray findings, and appear to be produced by anatomic abnormalities which cause turbulence of flow but which are not associated with any significant degree of shunting or obstruction. For example, a small ventricular septal defect may be associated with a loud well-localized murmur and a systolic thrill without evidence of increased heart size, hyperactive ventricles, or increased pulmonary vascularity, and with a normal pulmonary second sound and normal electrocardiogram. On catheterization studies, the shunt may be so small that one cannot confirm it by the oxygen content of the intracardiac samples. Such a lesion, although producing considerable noise, will show no evidence of imposing increased work load on the heart, and there is no reason to believe it will lead to pulmonary hypertension. There is no reason to limit the activity of a patient with this type of lesion; the only serious clinical implication under these circumstances is the threat of subacute bacterial endocarditis and appropriate precautions should be taken against this complication. Patients with idiopathic dilatation of the pulmonary artery which is seen radiologically, or a mild degree of pulmonary stenosis with which the right ventricle shows no evidence of overwork, should not be considered as having significant heart disease.

Dynamically significant heart disease is indicated by evidence of turbulence of flow, cardiac enlargement, shunting, or obstruction. It is best evaluated in terms of increased volume load in cases of shunting lesions, and of increased pressure load in those with obstruction and increased resistance to blood flow. This can be done with reasonable assurance clinically. Because the normal pressure in the right side of the heart and pulmonary arteries is much lower than that in the systemic circuit, uncomplicated septal defects and vascular connections between the two circuits always result in left-to-right shunts with increased pulmonary blood flow and increased volume load on the heart. Increased cardiac output, both in stroke volume and minute volume, are indicated clinically by cardiac enlargement, increased amplitude of the palpable cardiac impulse, and tachycardia.

A palpable thrill indicates turbulence of flow due to septal defect or an abnormal valve; the presence of a thrill does not, in itself, indicate dynamically significant heart disease. Heart enlargement usually is easily detected in young children with thin chest walls; it may be evident by precordial bulge or visible cardiac impulses. Palpation over the precordium will reveal increased amplitude of the heartbeat. The left ventricular impulse is maximal on palpation at or near the cardiac apex and is exerted anterolaterally. The right ventricular beat is felt along the right sternal edge as a "lift" or anterior motion. Large volume left-to-right shunt with greatly increased blood flow through the pulmonary artery gives rise to increased amplitude of the systolic impulse of the main pulmonary artery which can be palpated in the left second intercostal space at the sternal edge.

With left-to-right shunts, giving increased volume work to the heart, chest x-ray reveals increased pulmonary vascular markings and cardiomegaly, and the electrocardiogram usually shows ventricular hypertrophy of the so-called systolic overload type.

Regurgitant flow through incompetent valves also results in the signs of increased volume load.

Obstruction to flow is present in stenotic valve, hypertrophy of infundibular muscle, pulmonary hypertension, and coarctation of the aorta. The best single indication of the severity of obstruction to outflow of the right or left ventricles is the electrocardiogram, since dynamically significant obstruction is practically always associated with a definite ventricular hypertrophy pattern. On physical examination, there is a palpable thrill associated with a systolic crescendo-decrescendo murmur distal to the obstruction, over the main pulmonary artery in the left second intercostal space with pulmonary valve stenosis, and along the right upper sternal border with aortic valve stenosis. In children, however, the most prominent thrill and murmur of aortic stenosis, and sometimes the only impressive ones, are detected in the suprasternal notch rather than at the right sternal edge.

Right-to-left shunting mixes unoxygenated blood from the right side of the heart with the systemic arterial blood and is evidenced clinically chiefly by cyanosis and polycythemia. The heart may not be enlarged impressively on palpation or by x-ray, but the right ventricular impulse is increased and the electrocardiogram shows a definite pattern of right ventricular hypertrophy in most cases. In young children, iron deficiency anemia is relatively common and hemoglobin determination alone may not detect polycythemia since such a child may have a low or normal hemoglobin level with marked elevation of red blood cell count.

There are several dynamically significant lesions which, in children, may not be associated with striking clinical signs and which consequently may be missed or their importance not clinically appreciated. Most common of these are atrial septal defect, coarctation of the aorta, aortic stenosis, pulmonary hypertension, and cardiac decompensation as seen in infants.

The murmur of atrial septal defect is characteristically unimpressive in infancy and early childhood, even when there is a large volume shunt, and this diagnosis is commonly made in the later preschool or school-aged child rather than in the infant. The murmur may not be detected early or, if it is noted, is

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considered to be functional. There is usually no thrill, or a very soft one, over the pulmonary artery and the heart is not strikingly hyperactive on palpation. The child may be well developed and have no recognized exercise intolerance. On more careful examination, however, a distinct right ventricular lift can be felt with increased amplitude of the cardiac impulse; on auscultation, there is wide splitting of the second sound at the base of the heart. An electrocardiogram will usually show a pattern of incomplete right bundle branch block, sometimes with associated mild right ventricular hypertrophy, and x-ray of the chest will show an enlarged heart with increased pulmonary vascular markings.

Coarctation of the aorta, even of severe degree, is often overlooked in childhood because it may not give rise to a very impressive murmur, and because palpation of the pulses and determination of the blood pressure is not commonly done with care on routine examination of young children.

The murmur and thrill of aortic stenosis is usually audible and relatively prominent from early infancy, but may not be detected early when the maximal physical signs are located in the suprasternal notch rather than along the right upper sternal edge.

Pulmonary hypertension, associated either with shunts or as an isolated lesion, may not be appreciated in small children because there may be little or no murmur associated with it. The only really striking physical finding may be the palpably prominent and audibly increased pulmonary second sound heard in the left second or third interspace. On the electrocardiogram, right ventricular hypertrophy will be observed. An increased right ventricular impulse is palpable. The heart is usually not enlarged on x-ray examination.

Cardiac decompensation in infancy may be present without the physical signs which usually call attention to it in older patients. Pulmonary râles and peripheral edema are uncommon in heart failure in infancy. The primary indications are hepatomegaly, tachycardia, and respiratory distress.

The healthy-looking, vigorous child with a normal growth pattern, normal activity, a normal blood pressure, no evidence of cardiac enlargement or hyperactivity by physical signs, and no hypertrophy by electrocardiogram, even if he has a loud murmur, is in no need of definitive studies such as cardiac catheterization or angiograms, and need not be subjected to limitation of activity or special handling. He should, of course, be observed and examined periodically for any possible change of circulatory status. A child with evidence of large volume shunt, cyanosis, or more than a minor degree of obstruction will, of course, need further investigation and evaluation, with clinical recommendations based on his particular problem.

The same criteria of circulatory status are applicable to patients with history of suspected or definite rheumatic fever and to the child who has had heart surgery. If under these circumstances there is no evidence of heart enlargement, ventricular overactivity, valvular abnormalities, shunts, obstructions, or impaired myocardial function, the heart should be considered normal and no restrictions of activity imposed. Patients in whom there remains evidence of circulatory abnormality or cardiac strain must, of course, be individually evaluated and managed according to the degree of impaired function or heart strain.

Book Review

ENCYCLOPEDIA OF MEDICAL SYNDROMES. By Robert H. Durham, M.C., F.A.C.P. Forword by T. R. Harrison, M.D. New York, 1960, Paul B. Hoeber, Inc. Pp. 628, indexed. Price $13.50.

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"Syndromes" are more or less constant associations of signs and symptoms which are, in Dr. Durham's terms, of unknown etiology and hence not classified as "diseases." Dr. Durham quotes H. P. Hinsworth's observation that "the syndrome has, as its philosophical basis, not specific disease factors but a chain of physiological processes, interference with which at any point introduces the same impairment of bodily function. The same syndrome may thus arise from many different causes."

Science has not afforded us satisfactory information on even one cause of many of the syndromes described in this book. However, it is undeniable that it is the quest for such causes that, along with the frequent diversity of manifestations, lends excitement to the study of a patient affected by one of these complexes of signs and symptoms. As a result, the study of a compendium of syndromes, such as Dr. Durham's, is piquant.

On each of possibly 600 syndromes the book offers usually one to three paragraphs presenting the chief clinical manifestations, the laboratory and pathological findings, suggestions regarding etiology, the differential diagnosis, course, prognosis, and suggestions for treatment. Preference is given to the eponymic designation; however, the descriptive designation is consistently cross-indexed. The syndromes are also indexed under the organs involved.

The one or two references to reports presented in relation to each syndrome have been selected because "they supplied the best available summarization of the subject, aided in classifying questionable or controversial points, or provided an extensive bibliography." The reader with an historical bent may regret the author's frequent decision to omit the bibliographic reference to the original reports by the physicians whose names are honored by the eponyms. Possibly a future edition could supply this information. In addition, it could include in footnote form a sentence presenting biographical data on each eponymic ancestor. Thereby it could capitalize on one of the useful potentialities of eponymic nomenclature—a humanizing and emphasizing of the contribution to medicine of physicians of many countries and eras.

This well-organized and readable volume will be of interest and assistance to those concerned with diagnostic medicine, with the pathogenesis of disease, and, more specifically, with that blossoming field, medical genetics.

Palmer H. Futcher